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Review article

Role of cyclic nucleotides and their downstream signaling cascades in memory function: Being at the right time at the right spot

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ABSTRACT

A plethora of studies indicate the important role of cAMP and cGMP cascades in neuronal plasticity and memory function. As a result, altered cyclic nucleotide signaling has been implicated in the pathophysiology of mnemonic dysfunction encountered in several diseases. In the present review we provide a wide overview of studies regarding the involvement of cyclic nucleotides, as well as their upstream and downstream molecules, in physiological and pathological mnemonic processes. Next, we discuss the regulation of the intracellular concentration of cyclic nucleotides via phosphodiesterases, the enzymes that degrade cAMP and/or cGMP, and via A-kinase-anchoring proteins that refine signal compartmentalization of cAMP signaling. We also provide an overview of the available data pointing to the existence of specific time windows in cyclic nucleotide signaling during neuroplasticity and memory formation and the significance to target these specific time phases for improving memory formation. Finally, we highlight the importance of emerging imaging tools like Förster resonance energy transfer imaging and optogenetics in detecting, measuring and manipulating the action of cyclic nucleotide signaling cascades.

1. Introduction

Cyclic nucleotides are the “second messengers” that connect the extracellular environment to the intracellular environment and transduce the signal of the “first messenger” like hormones and neurotransmitters. The initial second messenger described was the cyclic adenosine monophosphate (cAMP) in 1971 by Earl W. Sutherland Jr. who won the ‘Nobel Prize in Physiology or Medicine’ for his discoveries concerning the “mechanism of the action of the hormones”. The same prize was awarded 27 years later to Robert F. Furchgott, Louis *J.* Ignarro and Ferid Murad for their work regarding the role of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) as signaling molecules in the cardiovascular system. The importance of cAMP in signal transduction was highlighted by the work of Eric Kandel who

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ATP, adenosine triphosphate; AC, adenylate cyclase; AKAP, A-kinase anchoring protein; AD, Alzheimer’s diasease; APP, amyloid precursor protein; β2-AR, β2-adrenergic receptor; BLUF, blue light utilizing flavin; BDNF, brain-derived neurotrophic factor; CaMK, calmodulin-dependent protein kinase; CaN, calcineurin; cAMP, cyclic AMP; CREB, cAMP response element binding protein; ChR, channelrhodopsin; COPD, chronic obstructive pulmonary disease; cpEGFP, circularly-permuted enhanced GFP; CR3control, region 3; CFP, cyan-fluorescent protein; cGMP, cyclic GMP; CNGC, cyclic nucleotide-gated channels; CNB, cyclic-nucleotide-binding; CA, Cornu Ammonis; DG, dentate gyrus; DEP, dishevelled, Egl-10, pleckstrin; DAG, diacylglycerol; DGC, diguanylate cyclase; DKO, double knock out; E-LTP, early-LTP; ERK, extracellular signal-activated kinase; Epac, exchange protein directly activated by cAMP; fEPSP, field excitatory postsynaptic potential; FLIM, Fluorescence Lifetime Imaging Microscopy; FRET, Förster resonance energy transfer; GSK-3glycogen, protein kinase 3; GPCR, G-proteins coupled receptors; GTP, guanosine triphosphate; GC, guanylyl cyclase; HR, halorhodopsin; HD, Huntington’s disease; HCN, Hyperpolarization-activated cyclic nucleotide–gated; ICUE, indicator of cAMP using Epac; IP3, inositol-1,4,5,triphosphate; KO, knock out; L-LTP, late-LTP; LAPD, light-activated PDEs; LOV, light-oxygen voltage; LTD, long-term depression; LTM, long-term memory; LTP, long-term potentiation; MSNs, medium spiny neurons; MAGUK, membrane-associated guanylate kinase; MWM, Morris Water Maze; MRP, multidrug resistant protein; NIRW, near-infrared window; NO, nitric oxide; NOS, nitric oxide synthase; NHR, N-terminal hydrophobic associated region; PD, Parkinson’s disease; PDE, phosphodiesterase; PLC, phospholipase C; PAC, photoactivated adenylate cyclase; I-1phosphatase, inhibitor-1; PIP2, phosphatidylinositol 4,5-biphosphate; PSD, postsynaptic density; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PKG, protein kinase G; PP1protein, phosphatase-1; pGC, particulate GC; REM, Ras-exchange motif; RA, Ras-association domain; STM, short-term memory; sGC, soluble GC; UCR, upstream conserved region; VASP, vasodilator-stimulated phosphoprotein; YFP, yellow-fluorescent protein

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Box 1
Different stages of plasticity and memory.

Synaptic potentiation represents an experimental model for examining the synaptic basis of learning and memory. Depending on the duration, synaptic potentiation can be divided into short-term potentiation (STP), lasting < 1 h, and long-term potentiation (LTP), lasting up to 8 h. Subsequently, LTP can be divided in 3 phases with distinct underlying mechanisms; LTP1 that dependents on activation of kinases, LTP2 that is the long-lasting phase and dependents on protein translation form pre-existing mRNA and LTP3 which requires gene transcription and subsequent protein translation (Bliss and Collingridge, 1993; Reymann and Frey, 2007). Early phase LTP (E-LTP) or LTP1 usually lasts less than 3 h while late LTP (L-LTP) or LTP3 could last up to 8 h. With respect to mnemonic stages, it is suggested that E-LTP is equivalent to short-term memory (STM) and L-LTP is related to long-term memory (LTM) (Izquierdo et al., 2002), while an intermediate-term memory (IM) phase is similar to LTP2. It could be proposed that STM could be converted to IM via early consolidation and from IM to LTM via late consolidation (Reneerkens et al., 2009).

described the importance of the synapses in memory formation, showing that activation of cAMP and its downstream kinases is essential for synaptic plasticity. Also Eric Kandel together with Arvid Carlsson and Paul Greengard received the 'Nobel Prize in Physiology or Medicine' for his seminal work on memory processes and function. Over the past decades, an abundance of studies emerged showing the role of cyclic nucleotides in cellular mechanisms related to memory function, including signal transduction, neuroplasticity, metabolism, gene transcription and cell growth (Box 1).

The present review will summarize available data and discuss the role of cyclic nucleotides in mnemonic processes. Additionally, upstream and downstream molecules involved in the cyclic nucleotide signaling cascade are discussed. Accordingly, the existence of time windows and their action is discussed, and the resulting significance to target specific windows in order to improve memory performance. Finally, we highlight the significance of emerging imaging tools in manipulating and determining the action of cyclic nucleotides signaling cascades.

2. Second messenger cascades

2.1. The cAMP pathway

The second messenger cAMP is synthetized from adenosine triphosphate (ATP) by adenylate cyclase (AC). ACs are transmembrane enzymes regulated by G-protein coupled receptors (GPCR). There have been identified nine unique membrane isoforms of AC, which are referred to as AC1-9, and one soluble form (sAC). Neurotransmitters can activate or inhibit AC signaling into the cells via GPCR. In basal conditions, GPCR are heterotrimers consisting of 3 subunits: α, β, γ. Activation of these receptors by their respective ligand (e.g. neurotransmitter or hormone) results in dissociation of the subunits into a free α subunit (G_{α}) and a free βγ subunit complex ($G_{\beta\gamma}$). The G_{α} can directly bind to AC, causing its activation ($G_{\alpha s}$) or inhibition ($G_{\alpha i}$). Increased production of cAMP triggers a multitude of cellular reactions coordinated by its downstream effectors, including protein kinase A (PKA), also named c-AMP dependent protein kinase (cAPK), cyclic nucleotide-gated channels (CNGC) and exchange protein directly activated by cAMP (Epac). Nevertheless, the most widely known and studied effector mediating intracellular cAMP signaling is PKA. Activated PKA can phosphorylate several cytosolic and nuclear substrates. A major event facilitating neuronal plasticity is phosphorylation and subsequent activation of cAMP response element binding protein (CREB) at Ser133 by PKA. Phosphorylated CREB (p-CREB) is an activated transcription factor that binds the cAMP response element (CRE), initiating the transcription of specific genes coding for neurotransmitter receptors such as ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors or growth factors including brain-derived neurotrophic factor (BDNF) (Bitner, 2012). Termination of PKA activity occurs via a negative feedback mechanism. Among the substrates that undergo phosphorylation by PKA are the phosphodiesterase enzymes (PDEs) that degrade cyclic nucleotides. Upon activation, PDEs catalyze the conversion of cAMP to ATP, reducing cAMP levels and bringing PKA back to its inactive state. PKA provides an additional negative feedback in the AC/cAMP signaling cascade by inhibiting the enzymatic activity of AC5 and AC6 (Chen et al., 1997; Iwami et al., 1995).

Despite the traditionally described AC/cAMP/PKA pathway that leads to CREB phosphorylation, it has been shown that cAMP/PKA could also indirectly lead to CREB phosphorylation via the extracellular signal-related kinase (ERK). In response to neurotransmitter release, the concentration of intracellular calcium (Ca^{2+}) is raised leading to the increased phosphorylation of ERK via the traditional Ras/Raf/MEK/ERK pathway (Impey et al., 1999). Subsequently, CREB is phosphorylated by the ERK-activated Rsk family of protein kinases (Impey et al., 1998; Xing et al., 1996). More precisely, Rsk2 is implicated in the Ca^{2+}-stimulated CREB phosphorylation in cell cultures (Impey et al., 1998). The impact of ERK on CREB phosphorylation is also supported by the observation that inhibition of ERK reduces CREB phosphorylation (Impey et al., 1998). Additionally, it has been shown in neuronal cell cultures that ERK could be activated in a Ras-independent fashion via PKA (Grewal et al., 2000). Based on that model, PKA was assumed to promote activation of the small G-protein Rap1 and the downstream kinase B-Raf creating the Rap1/B-Raf signaling complex that results in ERK activation (Grewal et al., 2000). However it is highly possible that Epacs also participate in the Rap1-mediated activation of ERK, since Rap-1 is activated by Epacs (Kitayama et al., 1989). This pathway could work in tandem with the previously described pathway in facilitating neuronal signaling upon an extracellular stimulus. Finally, except for the direct role of PKA in activating ERK, translocation of ERK to the nucleus requires PKA activity (Impey et al., 1998).

Additionally, there seems to be an interplay between the cAMP second messenger system and the phosphoinositol second messenger system. Binding of a ligand to the $G_{\alpha q}$-linked GPCR receptor leads to activation of phospholipase C (PLC) which hydrolyzes phosphatidylinositol 4,5-biphosphate (PIP2). The latter leads to the production of two intracellular mediators inositol-1,4,5,triphosphate (IP3) and diacylglycerol (DAG). IP3 diffuses rapidly into the cytosol and binds to the IP3 receptors of the endoplasmic reticulum, promoting the release of Ca^{2+}. DAG is retained in the membrane where it interacts with and activates protein kinase C (PKC) in the presence of Ca^{2+}. Of note, the source of Ca^{2+} could also be extracellular after stimulation of an ionotropic receptor [e.g. N-methyl-D-aspartate (NMDA) receptor]. Upon activation, PKC can activate ERK by acting on Raf as part of the Ras/Raf/MEK/ERK pathway (Ueda et al., 1996). Additionally, PKC stimulates activation of AC2, AC4, AC7 (Cooper, 2003; Schallmach et al., 2006; Tabakoff et al., 2001) and inhibits AC9 (Cumbay and Watts, 2004) creating a regulatory loop between PKC and cAMP/PKA signaling pathway. Elevated intracellular Ca^{2+} could also result in the activation of specific Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which can stimulate the insertion of AMPA receptors in the postsynaptic membrane (Sweatt, 1999). In addition, CaMKII can also activate PKA indirectly via activation of AC and subsequent production of cAMP (Mizunami et al., 2014).

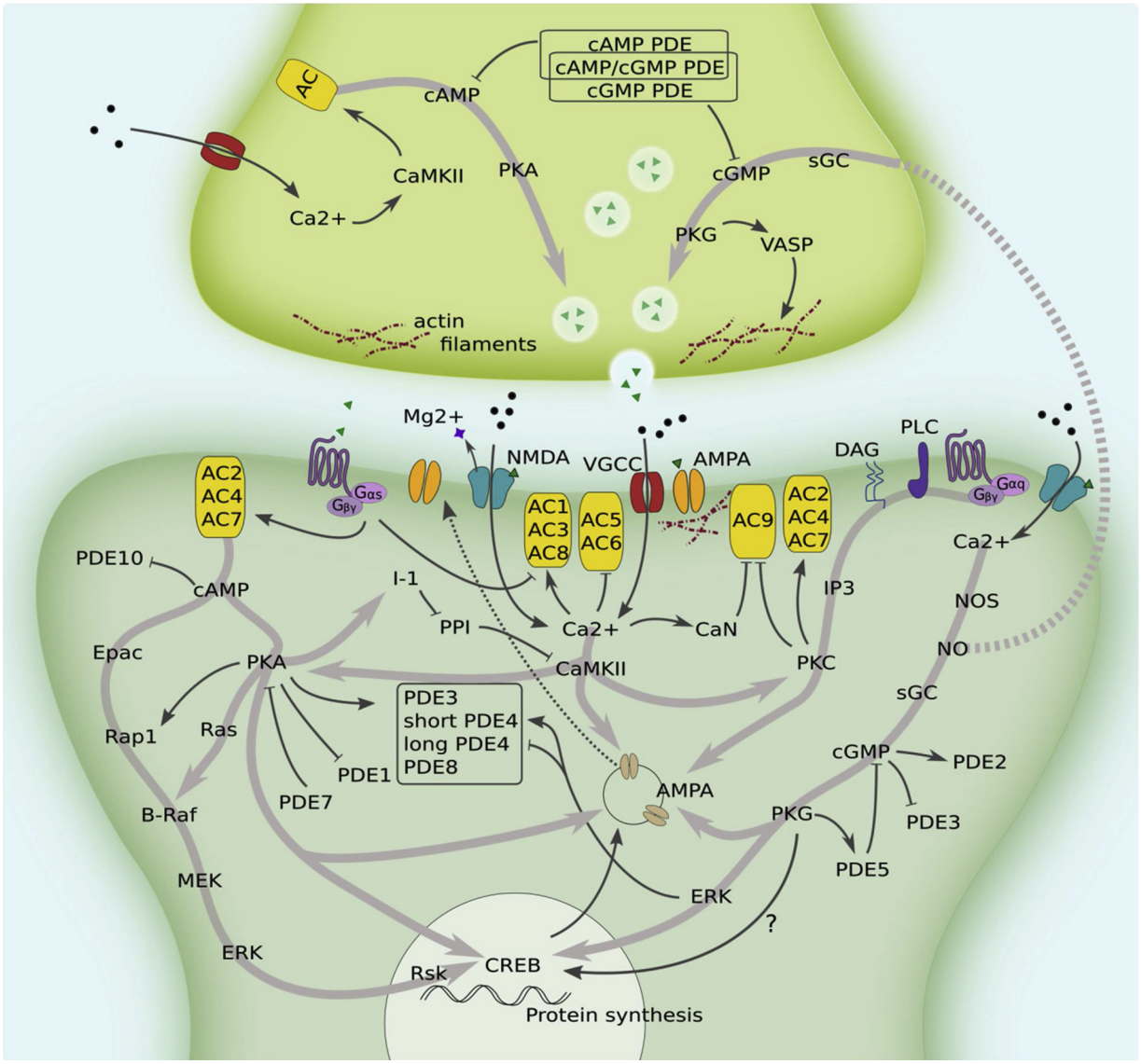

Fig. 1. Cyclic nucleotide signaling pathways at the pre- and post-synaptic cell. The cyclic adenosine monophosphate (cAMP) and cyclic guanylate monophosphate (cGMP) molecules are generated by the enzymes adenylate cyclase (AC) and guanylate cyclase (GC), respectively. The majority of ACs (AC1-9) is transmembrane and is regulated via G-protein coupled receptors (GPCRs). Binding of a neurotransmitter to GPCR could lead to dissociation of Gαs from the Gβγ subunit complex. In turn, binding of Gαs to ACs could lead to their activation. Apart from Gα, ACs are regulated by other molecules, leading to their classification into four groups. AC1, 3 and 8 (group I) are activated by Ca^{2+} and inhibited by Gβγ subunit. AC2, 4 and 7 (group II) are stimulated by Gβγ subunit and protein kinase C (PKC). AC5 and 6 (group III) are inhibited by Ca^{2+} and finally AC9 (group IV) is inhibited by calcineurin (CaN) and PKC.

Production of cAMP leads to activation of its downstream effectors exchange protein directly activated by cAMP (Epac) and protein kinase A (PKA) that will eventually promote protein synthesis via cAMP-responsive element binding protein (CREB). Another kinase that could phosphorylate CREB is extracellular signal-activated kinase (ERK). In addition to its activation by Ca^{2+}, ERK can be activated by the Rap1/B-Raf/MEK signaling complex. Rap1 can be activated either by PKA or by Epac, positioning ERK signaling downstream of cAMP. Apart from its role in long-term plasticity via induction of protein synthesis, PKA also participates in short-term plasticity. This is achieved via activation of the protein phosphatase inhibitor-1 (I-1) that relieves the inhibition of calmodulin-dependent protein kinase (CaMKII) from protein phosphatase-1 (PP1).

cGMP is produced by the enzyme GC that in the hippocampus exists mainly in a soluble form. The main ligand of soluble GC (sGC) is nitric oxide (NO), a gaseous molecule produced via the enzyme nitric oxide synthase (NOS). Production of cGMP leads to activation of protein kinase G (PKG) that upregulates CREB phosphorylation. Direct phosphorylation of CREB via PKG has been only shown *in vitro*. It is also suggested that PKG could promote CREB phosphorylation indirectly via ERK.

Another intracellular cascade that interacts with the cyclic nucleotide cascade is the phosphoinositol second messenger system. Binding of a ligand to the Gαq-linked GPCR receptor leads to activation of phospholipase C (PLC) that eventually promotes the production of two intracellular mediators; inositol-1,4,5,triphosphate (IP3) and diacylglycerol (DAG). IP3 facilitates the release of Ca^{2+} from intracellular compartments, whereas DAG activates PKC. Increase in intracellular Ca^{2+} levels could also result from stimulation of the N-methyl-D-aspartate (NMDA) receptor or the voltage-gated calcium channels (VGCC). Elevated Ca^{2+} into the cell facilitates activation of CaMKII that could subsequently activate the cAMP signaling cascade.

A point of convergence of the above cascades in the post-synaptic cell is the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. PKA and PKG phosphorylate AMPA receptors at the same site (S845) promoting their trafficking to the synapse. Additionally, insertion of AMPA receptors into the membrane is facilitated by their phosphorylation by CaMKII and PKC. Finally, new AMPA receptors are synthesized after CREB activation.

Major regulation of the intracellular concentration of cyclic nucleotides is provided by phosphodiesterases (PDEs), a family of eleven members (PDE1-11) that hydrolyzes cAMP and/or cGMP. The dual substrate PDE1, 2, 3, 10, 11 could degrade both cyclic nucleotides, while PDE4, 7, 8 are cAMP-specific and PDE5, 6, 9 are cGMP-specific.

At the pre-synaptic cell, activation of cAMP and cGMP cascades could lead to release of neurotransmitters, more specifically glutamate (green triangles), at the

synaptic cleft. AC is activated via Ca^{2+} /CaMKII, while sGC is activated by NO that is produced in the postsynaptic cell and acts as a retrograde messenger to the pre-synaptic cell. Activated PKG could phosphorylate vasodilator-stimulated phosphoprotein (VASP) at both the pre-and post-synaptic cell (not shown) regulating actin polymerization. As with the post-synaptic cell, the main regulation of cyclic nucleotide concentration at the pre-synaptic cell is provided by PDEs.

Table 1
Summary of the different types of adenylate cyclases, their differential regulation, region-specific expression and function in the brain. AC = adenylate cyclase, CA1 = Cornu Ammonis 1, CaMK = calmodulin-dependent protein kinase, DG = dentate gyrus.

Type	Group	Isoform	Regulation	Hippocampal/brain expression	CNS function
Membrane-bound AC	Group 1	AC1, AC3, AC8	Ca^{2+}, CaMK, synergistically activated by $G_{\alpha s}$, inhibited by $G_{\beta\gamma}$	AC1, AC3, AC8 highly expressed in CA1 subregion; AC1 also expressed in DG	Diverse, including memory
	Group 2	AC2, AC4, AC7	Ca^{2+} insensitive, stimulated by $G_{\beta\gamma}$	AC2 in DG; AC4 in brain but mainly in vessels; AC7 not in brain	Diverse, including memory
	Group 3	AC5, AC6	Inhibited by Ca^{2+} and the $G_{\alpha i}$	AC5 and AC6 are mainly expressed in the CA2 subregion	Diverse, including memory
	Group 4	AC9	Unresponsive to forskolin, negatively regulated by calcineurin	AC9 highly expressed in all three CA subregions and in the DG	Diverse, including memory
Soluble AC	n.a.	Only 1 soluble form	Activated by bicarbonate	Nucleus, mitochondria and centrosome	Cell division

Except for the above mechanisms that represent the postsynaptic action of the cAMP signaling pathway, a presynaptic role has also been identified. Presynaptically, cAMP is mainly involved in synthesis, release and metabolism of neurotransmitters like glutamate and dopamine (Rodríguez-Moreno and Sihra, 2013; Schoffelmeer et al., 1985), most likely via a presynaptic CaMKII/AC/cAMP/PKA cascade. Additionally, presynaptic cAMP levels are also regulated by GPCRs independent of CAMKII, including metabotropic glutamate receptors (Schoepp, 2001) and cannabinoid receptors (Alonso et al., 2017; Chevaleyre et al., 2007) (Fig. 1).

2.2. The cGMP pathway

In the same line as cAMP, cGMP production is catalyzed by the enzyme guanylate cyclase (GC) from guanosine triphosphate (GTP). GC exists in two forms; either a membrane bound particulate GC (pGC) or a soluble GC (sGC) form. The seven isoforms of pGC are mainly expressed in the periphery and their distribution in the brain is restricted to the pineal gland, the cerebellum, the pituitary and the olfactory epithelium. sGC is widely distributed in the brain including the hippocampus, striatum, cerebral cortex and locus coeruleus (Matsuoka et al., 1992). In the brain, intracellular responses to neurotransmitters are mainly attributed to activation of sGC, while the pGC responds to natriuretic peptides (Schulz et al., 1991). It has been proposed that several neurotransmitters could activate sGC for the production of cGMP. However the most potent activator is NO which is synthesized from the enzyme nitric oxide synthase (NOS) in response to elevated Ca^{2+} levels. Ca^{2+}/calmodulin binds to the catalytic domain of NOS which catalyzes the synthesis of NO from L-arginine. At nanomolar concentrations, NO binds to sGC and rapidly increases the catalytic conversion of GTP to cGMP (Ignarro et al., 1982; Stone and Marletta, 1996). The main intracellular effectors conveying the NO-sGC signal include cGMP-gated cation channels, protein kinase G (PKG; or cGMP-dependent protein kinase (cGK)) and phosphodiesterases (cGMP-specific phosphodiesterases and cGMP-regulated phosphodiesterases that have allosteric sites for cGMP). From the effectors above, PKG has been most extensively studied and several lines of evidence implicate the cGMP/PKG pathway in the modulation of synaptic transmission.

NO acts as retrograde messenger and stimulates presynaptic sGC to induce production of cGMP, which eventually leads to the production of PKG. Additionally, in the presynaptic terminal, cGMP can influence the release of neurotransmitters, like glutamate and dopamine (Arancio et al., 1996; Sanchez et al., 2002). Postsynaptically it has been shown that upregulation of the cGMP/PKG pathway results in CREB phosphorylation (Lu and Hawkins, 2002; Lu et al., 1999). The underlying mechanism of this relationship is yet elusive. *in vitro* studies conducted with cell lines showed that, although PKG could phosphorylate a synthetic peptide of CREB that contains the Ser133 sequence, the reaction occurs at a lower rate in comparison to PKA (Colbran et al., 1992). Therefore, the general belief is that the cGMP/PKG pathway mediates CREB phosphorylation via an indirect mechanism, which is also supported by the fact that there is no evidence showing PKG nuclear localization. PKG could also facilitate CREB phosphorylation by stimulating the release of Ca^{2+} from ryanodine-sensitive stores (Lu and Hawkins, 2002). In that respect, CREB phosphorylation can be mediated by Ca^{2+}-sensitive ERK via the CREB kinase Rsk2 (Impey et al., 1998). Finally, PKG has been shown to stimulate polymerization of actin filaments at both pre- and post-synaptic cells, regulating aggregation of synaptic molecules, e.g. AMPA receptors at the post-synaptic cell (Wang et al., 2005a) (Fig. 1).

3. Adenylate cyclases: regulation, tissue distribution and participation in neuronal function

ACs are the key enzymes in the initiation of cAMP signaling since they catalyze the conversion of ATP to cAMP. Based on their regulation, membrane-bound ACs can be divided in four groups (Table 1). Group I consists of AC1, AC3 and AC8, which are activated by Ca^{2+} and CaMKII. Additionally, they are synergistically activated by $G_{\alpha s}$ (Cali et al., 1996; Krupinski et al., 1992; Tang and Gilman, 1991), while they are inhibited by $G_{\beta\gamma}$ (Steiner et al., 2006; Tang and Gilman, 1991; Tang et al., 1991). Although AC3 is grouped along with AC1 and AC8 as Ca^{2+}-activated AC, this classification is based on one study showing that AC3 can be activated by high levels of Ca^{2+}, but only when the co-factors forskolin or GppNHP (a non-hydrolysable GTP analog) are present (Choi et al., 1992). The fact that in cell lines only AC1 and AC8 are stimulated in physiologically relevant concentrations of Ca^{2+}, questions the co-categorization of AC3 in the same group as AC1 and AC8 (Fagan et al., 1996). Group II contains the Ca^{2+} insensitive AC2, AC4 and AC7, which are stimulated by $G_{\beta\gamma}$ subunits (Feinstein et al., 1991; Gao and Gilman, 1991; Tang and Gilman, 1991; Yoshimura et al., 1996). Group III contains AC5 and AC6 which are inhibited by Ca^{2+} and the $G_{\alpha i}$ (Ishikawa et al., 1992; Katsushika et al., 1992; Premont et al., 1992; Yoshimura and Cooper, 1992), and group IV contains AC9, which is the only AC isoform that is not responsive to forskolin, and undergoes negative regulation by calcineurin (CaN) (Antoni et al.,

1998; Paterson et al., 1995) (Fig. 1). Finally, the sAC is located in the nucleus, mitochondria and centrosome during cell division and it is activated by bicarbonate. Changes in bicarbonate reflect changes in pH and carbon dioxide indicating that unlike membrane AC that responds to extracellular signals, sAC responds to intrinsic cellular signals (Zippin et al., 2003).

A detailed analysis of the expression of the different AC isoforms in mouse brain, revealed that all isoforms are expressed in neuronal tissue with the exception of AC7, which is undetectable in the brain, and AC4 that is mainly expressed in vessels (Visel et al., 2006). With respect to their expression pattern in the hippocampus, it was shown that AC1, AC2 and AC8 are highly expressed in Cornu Ammonis 1 (CA1), while AC1 and AC2 are also expressed in dentate gyrus (DG). AC5 and AC6 are mainly expressed in the CA2 subregion. Interestingly, AC9 is abundant in the hippocampus and it is the only isoform highly expressed in all three CA subregions and in the DG (Antoni et al., 1998). Based on the above observation, the authors suggested regional co-localization and complementation in the expression pattern of ACs that share the same regulatory mechanism in the hippocampus. Additionally, there seems to be complementation in the expression of group I ACs, with AC1 expression prevailing in the DG, while AC8 is mainly restricted to CA1. Except for the distinct cellular localization, AC1 and AC8 also display distinguished patterns of subcellular expression. In particular, AC1 is abundantly expressed in the postsynaptic density and extrasynaptic sites, whereas AC8 is mainly expressed in the presynaptic active zone and extrasynaptic fractions (Conti et al., 2007). Despite the importance of the above findings regarding the expression of AC, they do not provide evidence for the expression of functional AC enzymes in the different subregions of the hippocampus (Visel et al., 2006; Willoughby and Cooper, 2007).

3.1. Role of ACs in synaptic plasticity and memory

ACs have been shown to be involved in plasticity and hippocampus-dependent forms of memory. Consistent with their expression and distribution in the hippocampus, the involvement of the Ca^{2+}-stimulated AC1 and AC8 is extensively studied in LTP studies and behavioral paradigms. Mice that overexpress the AC1 encoding gene Adcy1 showed sustained LTP (e.g. L-LTP) after an induction protocol that normally induces only E-LTP (Wang et al., 2004), and additionally exhibited impairments in long-term depression (LTD) (Zhang and Wang, 2013). This observation was accompanied by a pro-cognitive effect in the object recognition test (ORT), in which transgenic mice were able to remember the objects after a long interval between the two trials (Wang et al., 2004). These results indicate that increased activation of AC1 could convert the initial short-term memory (STM) into a more stable long-term memory (LTM) that lasts up to days. Additionally, the Adcy1-overexpressing mice exhibited lower rates of fear memory extinction. The authors attributed the latter finding to increased ERK and CREB phosphorylation that could result in enhanced initial memory formation and therefore hampered extinction (Wang et al., 2004). Intriguingly, another study showed that AC1-overexpressing mice showed better memory flexibility in a spatial memory task, as reflected by their ability to suppress previously learned information and relearn the task, indicating that the extinction mechanism appears to differ in fear and spatial memory (Zhang and Wang, 2013).

Noteworthy is a study from Storm and colleagues in which they examined the effect of AC1 overexpression in both young and aged mice (Garelick et al., 2009). As it was expected, young mice showed a superior mnemonic ability in comparison to their aged littermates in several mnemonic tasks including fear conditioning, object recognition and spatial memory. Interestingly, AC1 overexpression in aged mice did not affect their performance in the first two tasks and even resulted in memory deficits in spatial memory. Considering that basal levels of AC1 activity were downregulated with aging, the above finding seems initially counterintuitive. Nevertheless, it was also shown that in the aging brain PKA activity is also downregulated in certain brain areas (Arnsten et al., 2005; Ramos et al., 2003).Therefore, the negative effect of AC1 overexpression could be possibly attributed to hyperstimulation of the cAMP pathwayinagedanimals.

Except for overexpression of the gene, a reversed approach was also employed in order to investigate the role of Ca^{2+}-stimulated ACs in plasticity and memory. Early studies showed that knockout (KO) of AC1 impaired the mossy fiber (DG→CA3) LTP, while the perforant path (entorhinal area→DG) and the Schaffer collateral (CA3→CA1) LTP were unaffected (Villacres et al., 1998). Despite the fact that AC8 contributes in lesser extent than AC1 to Ca^{2+}-stimulated ACs activity in the hippocampus, AC8 KO mice manifested the same level of impairments in mossy fiber LTP as AC1 KO mice (Wang et al., 2003). Although genetic depletion of either AC1 or AC8 did not impair the Schaffer collateral LTP in the hippocampus, double KO (DKO) mice for both genes showed deficits in this type of LTP (Wong et al., 1999). DKO mice also failed to express LTD (Zhang et al., 2011), suggesting that the action of both Ca^{2+}-stimulated ACs is important for bidirectional synaptic plasticity.

At the behavioral level, KO mice for either AC1 or AC8 displayed deficits in the Morris water maze (MWM) spatial learning task (Wu et al., 1995; Zhang et al., 2008). It appears to be a redundancy in the function of these two isoforms since AC1 or AC8 KO mice did not exhibit memory impairments in passive avoidance learning and contextual fear conditioning, while DKO had impaired performance in these tasks (Wong et al., 1999). Importantly, although AC1 KO mice exhibited normal acquisition and retrieval of contextual fear memory, they were unable to sustain it for a long period in comparison to wild type mice, pointing out the importance of AC1 for memory stability (Shan et al., 2008). The differential effect of AC1 or AC8 KO mice in comparison with DKO mice in various learning tasks could be related to the involvement of different brains areas during each task, as well as with the distinct distribution of the different Ca^{2+}-stimulated ACs in the subregions of the hippocampus. For example, it was suggested that the mRNA of AC1 was increased in the subregion CA1-CA2 of the hippocampus during the acquisition phase of radial arm water maze (e.g. a derivative of MWM that assesses reference spatial memory), but not during the procedural version of the task (Mons et al., 2003). This regional specificity indicates that formation of spatial and non-spatial memory requires distinct distribution of Ca^{2+}-stimulated ACs in the hippocampus (Mons et al., 2003). Finally, impairments in DKO mice were accompanied by deficits in relearning and suppression of old spatial memory in the reversal platform test of MWM, outlining again the importance of balanced cAMP/PKA signaling for strengthening and weakening of the synapses (Zhang et al., 2011).

Although studies examining the involvement of AC1 or AC8 isoforms in plasticity and memory are prevailing, AC3 seems to possess a unique role in mediating signal transduction. This notion was supported by its high expression in neuronal cilia (Bishop et al., 2007). Specifically, in the hippocampus, AC3 is only expressed in the primary cilia of neurons (Wang et al., 2011). Although the exact role of neuronal cilia in memory remains elusive, it is hypothesized that neuronal cilia represent signaling platforms, sub-serving interactions between receptors (Green and Mykytyn, 2014). It was shown that AC3 KO mice display severe deficits in short-term object recognition memory. Additionally, the transgenic mice showed no impairment in a contextual fear conditioning paradigm, but were unable to dissociate the context with the foot-shock during the extinction paradigm (Wang et al., 2011). Therefore, the AC3 KO mice appear to have a similar behavioral phenotype with the AC1 and AC8 KO mice, showing impaired acquisition of spatial memory and extinction of fear memory. Altogether, these findings suggest a novel role of AC3 in conjugation with the already established role of AC1 and AC8 in neuronal function underlying mnemonic processes.

Table 2
Summary of the different types of protein kinase A, their region-specific expression and function in the brain. PKA = protein kinase.

Group	Regulatory domain subunits	Expression	CNS function
PKAI	RIα and RIβ	Neocortex, caudate-putamen, hypothalamus, thalamus, hippocampus	Diverse, including memory
PKAII	RIIα and RIIβ	Medial habenula, hippocampus, thalamus	Diverse, including memory

4. Role of PKA in synaptic plasticity and memory

Each PKA is a holoenzyme, consisting of two regulatory (R) and two catalytic (C) domains. The PKA family is comprised of four R (RIα, RIβ, RIIα, RIIβ) and three C (Cα, Cβ, Cγ) subunits. The division of PKA into two classes, PKAI (consisting of RIα and RIβ dimers) and PKAII (consisting of RIIα and RIIβ dimers) has been attributed to the differences in the R subunits (Table 2). Refined crosstalk between the different intra-domains of the R subunits ensures efficient regulation of PKA activity in response to cAMP (McNicholl et al., 2010). Additionally, binding of cAMP in the two R domains, causes conformational changes leading to the dissociation of the C subunits from the R subunits (Gibbs et al., 1992; Taylor et al., 1990). Subsequently, the C subunits could translocate to the nucleus where they catalyze phosphorylation of serine and threonine residues of several proteins (Abel and Nguyen, 2008). In addition, recent evidence showed that there is a functional pool of PKA tetramers in the nucleus that contributes to fast nuclear PKA signaling (Sample et al., 2012). Since the pioneering work of Kandel in *Aplysia* showing the necessity of PKA for consolidation of long-term memories, several studies established the involvement of PKA signaling in plasticity and memory in rodents. More precisely, a great body of literature supports that PKA activity is important for L-LTP in hippocampal slices. This observation is supported by both pharmacological and genetic models showing that inhibition of PKA activity can suppress expression of L-LTP (Huang and Kandel, 1994; Impey et al., 1996; Nguyen and Kandel, 1997) and conversely PKA activation can elicit L-LTP (Bach et al., 1999; Frey et al., 1993). Nguyen and Kandel showed that application of the two different PKA inhibitors KT-5720 (inhibits the catalytic subunit) and Rp-cAMPS (inhibits the regulatory subunit) during the induction of LTP leads to a rapid decline in the amount of potentiation (Nguyen and Kandel, 1997). Nevertheless, LTP was unaffected when the inhibitors were applied 30 min after induction, indicating that PKA recruitment is essential during a defined time window (Nguyen and Kandel, 1997). Additionally, LTP was declined in the transgenic mouse model *R(AB)*, that expresses a dominant inhibitory form of the regulatory subunit of PKA (Abel et al., 1997), while in mice lacking the $C\beta_1$ isoform of the Cβ subunit, L-LTP was attenuated 2.5 h after the induction (Qi et al., 1996). Although the above studies implicate the action of PKA at the L-LTP, the study of Otmakhova et al. supported the idea that the action of PKA at the postsynaptic cell is not only restricted to L-LTP, but it is also important for expression of E-LTP (Otmakhova et al., 2000).

Based on these later observations PKA activity could be involved in both E-LTP and L-LTP and its action is mediated via phosphorylation of different substrates. Regarding its role in L-LTP, PKA action seems to be mediated by CREB phosphorylation and subsequent transcription of new proteins involved in plasticity (Matsushita et al., 2001; Nguyen et al., 1994). The mechanism by which PKA is involved in E-LTP is more unclear, but is thought to require phosphorylation of existing substrates like AMPA and NMDA receptors. Bidirectional trafficking of AMPA receptors is important for hippocampal synaptic plasticity and memory formation (Derkach et al., 2007; Hu et al., 2007; Malenka, 2003). During LTP, PKA-dependent phosphorylation of GluA1-AMPA receptors at Ser845 is required for stable LTP and incorporation of GluA1-AMPA receptors at the synaptic site is blocked by PKA inhibitors (Esteban et al., 2003). Similarly, PKA activity is also linked to NMDA receptor phosphorylation and it was shown that phosphorylation of NMDA receptors by PKA would alter Ca^{2+} influx via the channel (Skeberdis et al., 2006).

Apart from the above substrates, activated PKA could facilitate signal transmission during E-LTP by modulating the activity of protein kinases and phosphatases. PKA indirectly promotes CaMKII phosphorylation by blocking the activity of protein phosphatase-1 (PP1) through activation of its endogenous blocker protein phosphatase inhibitor-1 (I-1) (Blitzer et al., 1998, 1995). Negative feedback in the above cascade is provided by Ca^{2+}-activated CaN that inhibits I-1 activity and subsequently CaMKII phosphorylation (Yakel, 1997).

As with LTP experiments, a variety of rodent behavioral studies verified that intact PKA signaling is important for formation of LTM. Disruption of PKA activity either via genetic or via pharmacological intervention resulted in impairments in long-term spatial memory (Abel et al., 1997; Sharifzadeh et al., 2005), contextual memory (Abel et al., 1997; Ahi et al., 2004; Bourtchouladze et al., 1998; Wallenstein et al., 2002) and aversive memory (Bernabeu et al., 1997a; Quevedo et al., 2004; Vianna et al., 2000). It was also shown that PKA activity occurs immediately after training in certain mnemonic tests suggesting it to play a role in STM. Specifically, PKA and p-CREB immunoreactivity were increased in the hippocampus immediately, 3 h and 6 h after training in the step-down inhibitory test, while intra-hippocampus infusion of the PKA inhibitor KT5720 immediately or 3 h or 6 h post-training impaired the consolidation process of the task (Bernabeu et al., 1997a). Similarly, two different studies measured PKA levels in the hippocampus during spatial learning and showed that PKA immunoreactivity increases rapidly during training and remained high at later stages of the acquisition phase (Mizuno et al., 2002; Vázquez et al., 2000).

A later study from Havekes et al. sought to determine the region specific changes in the RIIα,β subunits of PKA in the hippocampus during habituation, training and reversal training in the Y-maze task (Havekes et al., 2007). Habituation increased PKAIIα,β non-specifically in all the regions of the hippocampus, suggesting that PKA expression is elevated at the initial storing phase of spatial memory. During training and reversal training (day 3) PKAIIα,β expression was increased in CA3 region and DG, while at the end of the procedures (day 7) immunoreactivity of PKAIIα,β returned to basal levels. These results indicate that PKA expression in the hippocampus is essential for the acquisition and consolidation of new information, initiating molecular cascades that eventually will facilitate formation of stable LTM (Havekes et al., 2007).

Despite the fact that PKA activation facilitates consolidation of memories in the hippocampus, it was shown that activation of the cAMP/PKA signaling cascade in the prefrontal cortex could have a differential effect (Arnsten et al., 2005). Although upregulation of the cAMP/PKA pathway could improve performance in memory-dependent tasks, infusion of a PKA activator in the prefrontal cortex of young rats induced a dose-dependent deficit in delayed-alternation performance (Taylor et al., 1999). This observation was more profound in aged animals in which cAMP/PKA signaling is reduced in the hippocampus, while it is elevated in the prefrontal cortex. Consistent with this observation, a PKA activator (Sp-cAMPS) impaired working memory in aged rats, while low doses of a PKA inhibitor (Rp-cAMPS) had the opposite effect (Ramos et al., 2003). Interestingly, the beneficial effect of PKA inhibition was more intense in animals with greater memory deficits due to aging. These observations suggest the importance of taking into consideration age-related and region-specific biochemical differences when examining the cognitive enhancing properties of drugs that

Table 3
Summary of the different isoforms and splice variants of Epacs and their tissue-specific expression. Epac = exchange protein directly activated by cAMP.

Isoforms	Splice variant	Expression
Epac1	Epac1	Widely distributed
Epac2	Epac2A + Epac2B	Cortex, hippocampus, habenula, cerebellum, adrenal glands

act on the cAMP/PKA pathway.

5. Role of Epacs in modulating cAMP signaling

The discovery of Epacs brought a new perspective to the prevailing view that PKA is the only downstream effector for cAMP signaling. There are two isoforms of Epac, i.e. Epac1 and Epac2 (Epac2A and Epac2B), produced by their two respective genes (Table 3). The C-terminal catalytic region is the same for both Epacs and it is composed of 3 domains: i) a Ras-exchange motif (REM) domain, ii) a Ras-association (RA) domain and iii) a GEF domain responsible for Epac exchange activity on Raf GTPases (De Rooij et al., 2000). The regulatory N-terminus contains a dishevelled, Egl-10, pleckstrin (DEP) domain responsible for membrane binding and a cyclic-nucleotide-binding (CNB) domain that binds cAMP with high affinity (De Rooij et al., 2000;, 1998). Although Epac1 and Epac2B have one CNB-B domain, Epac2A has an additional CNB-A domain at the N-terminus. Despite that difference, CNB-A binds cAMP with very low affinity in comparison to CNB-B, and does not contribute significantly to Epacs' regulation by cAMP (Rehmann et al., 2003). Similarly to PKA, binding of cAMP to the regulatory domain of Epacs leads to their activation. Subsequently, Epacs activate the small GTPases Rap1 and Rap2 that represent their main downstream effector (Kitayama et al., 1989). The tissue distribution of Epac1 and Epac2 differs since Epac1 appears to be widely distributed, while Epac2 is mainly expressed in the brain and the adrenal glands. Regarding their pattern of expression in the rat brain, mRNA of Epac1 is abundantly expressed, but generally at low levels, whereas the mRNA of Epac2 is highly expressed in certain regions including cortex, hippocampus, habenula and cerebellum (Kawasaki et al., 1998). At the subcellular level, Epacs are mainly localized in the nuclear membrane and mitochondria, while during cell division they are located to the mitotic spindle and centrosome (Qiao et al., 2002).

Through their effectors, Epacs can orchestrate several cellular functions raging from gene transcription to cell proliferation and apoptosis, and additionally regulate several intracellular pathways and signaling processes. For example, downstream activation of ERK and P13-kinase-dependent PKB/Akt pathway via Epacs, introduces an important link between Epac action and memory processes (Grandoch et al., 2010). Both electrophysiological and behavioral studies suggest the importance of Epacs in plasticity. Perfusion of mouse hippocampal slices with the Epac agonist 8-(4-chlorophenylthio)-2′-O-methyl-cAMP (8-pCPT) enhanced the maintenance of LTP induced by a weak tetanus, without affecting the initial magnitude of potentiation. This effect was shown to depend on ERK phosphorylation and protein synthesis, while blockage of transcription and PKA activity did not abolish 8-pCPT-dependent facilitation of LTP (Gelinas et al., 2008). These results suggest that Epac activation initiates ERK signaling that subsequently promotes local translation of a pre-existing pool of dendritic mRNAs (Gelinas et al., 2008). Additionally, it has more recently been shown that Epac plays an important facilitating role in cerebellar Purkinje cells during LTP and motor learning (Gutierrez-Castellanos et al., 2017). It appears that Epacs comprise a dual function in synaptic transmission since it was shown that, except for the observed enhancement of synaptic transmission, activation of Epacs could also induce LTD in hippocampal slices. This function was shown to be dependent on activation of the p38-mitogen activated protein (MAP) kinase pathway and on internalization of GluA2/3-containing AMPA receptors (Ster et al., 2009). Considering that PKA was shown to facilitate LTP in the hippocampus (Frey et al., 1993), the latter finding regarding Epac-dependent LTD provides an additional pathway in the already established role of cAMP signaling cascade in synaptic plasticity. Nevertheless, it still remains unanswered which cellular components determine which pathway will be activated in response to cAMP. Considering that PKA and Epacs have the same affinity for cAMP in living cells, it was hypothesized that subcellular compartmentalization or substrate availability determine which downstream effector will be activated by cAMP (Ster et al., 2009).

Consistent with the electrophysiological findings, the role of Epacs in memory formation was supported by behavioral studies. Most importantly, it was shown that Epacs participate in distinct stages of memory formation. Intracerebroventricular (ICV) administration of 8-pCPT 1 h after the fear conditioning paradigm improved mice performance (Kelly et al., 2009). Similarly, intrahippocampal infusion of the Epac agonist immediately after fear conditioning facilitated memory formation and it was able to attenuate PKA antagonist-induced memory impairments (Ma et al., 2009). Another study, that tried to gain more insight into the distinct memory stages during which Epac activation can facilitate memory, supports the idea that their intrahippocampal activation facilitate contextual fear memory when it takes place at the stage of retrieval, but not at the acquisition phase (Ostroveanu et al., 2010). Additionally, it was shown that Epac2 is the responsible isoform for the enhancing effects of Epac's activation on memory retrieval, since silencing of Epac2 via intrahippocampal injection of siRNA impaired memory retrieval (Ostroveanu et al., 2010).

Although there is scarce of evidence, a few studies support a promising role of Epacs as a target in neurodegenerative diseases. For example, in neuronal cell cultures, Epac1 can exhibit neuroprotective action against the neuropathological features of Alzheimer's disease (AD). Specifically, activation of Epac1 after stimulation of the G_s-coupled serotonin receptor could promote activation of the small GTPases Rap1 and Rac1. This activation of the Epac1-Rap1-Rac1 signaling cascade increased the cleavage of the amyloid precursor protein (APP) via the α-secretase pathway (Maillet et al., 2003; Zaldua et al., 2007), leading to the release of soluble APPα (sAPPα) at the extracellular space (Robert et al., 2005). Importantly, it was shown that sAPPα has promising cognitive enhancing and neuroprotective properties (Allinson et al., 2003). These observations are particularly important because they could extend our knowledge regarding AD pathology and suggest novel targets for the treatment of the disease. Regarding the role of Epac2 in neurodegenerative diseases, it is reported that Epac2 activation via 8-pCPT influences dendritic spine remodeling, and mutations in the EPAC2 gene could contribute to brain disorders (Woolfrey et al., 2009). Nevertheless, there is no further evidence supporting the cognitive enhancing properties of Epac2 in AD.

6. Hyperpolarization-activated cyclic nucleotide–gated (HCN) channels

Another class of cyclic nucleotide receptors are the hyperpolarization-activated cyclic nucleotide–gated (HCN) channels. HCN channels are important membrane proteins that serve as nonselective voltage-gated cation channels (Sartiani et al., 2017). As their name states, they open at hyperpolarization potential and are regulated by cyclic nucleotides (mainly cAMP). They conduct Na^+ and K^+ ions and are mainly known for their pacemaking activity in cardiac cells, but are also expressed in the brain where they can be found in neurons of the hippocampus (He et al., 2014). The HCN family consists of four isoforms (HCN1–4), all of which have been found in mouse or human brain tissue. HCN1 is highly expressed in the neocortex, hippocampus, cerebellar cortex, brainstem, and spinal cord. HCN2 is widely distributed throughout the brain, but it is especially abundant in thalamic

and brainstem nuclei. The expression of HCN3 is limited and quite scattered throughout the brain. HCN4 expression is strong in areas such as the olfactory bulb and the thalamus, with a distribution pattern that appears complementary to that of HCN1 (Sartiani et al., 2017).

The potential impact of HCN channels on plasticity mechanisms and memory formation is supported by a limited number of studies. For instance, in the dendritic compartment of hippocampal CA1 pyramidal neurons, the effect exerted by HCN current limits the activation of voltage-dependent Ca^{2+} entry, with important consequences on synaptic excitability (Tsay et al., 2007). This way, LTP and memory function are constrained by normal HCN function. Indeed, HCN1-KO mice show improved hippocampal-dependent learning and memory performance. In these mice, proximal synapses (CA3–CA1 contacts) function normally, whereas they are potentiated at distal locations (EC layer III–CA1 contacts), as predicted by stronger expression of HCN channels in this compartment (Nolan et al., 2004). These effects were accompanied by improvements in spatial memory performance. Similarly, LTP was significantly increased in the perforant path of HCN2 KO mice (Matt et al., 2011), while global KO of HCN3 had no significant spatial learning deficits in comparison with control mice (Stieglitz et al., 2018). Together, these early studies indicate therapeutic potential for HCN channels as targets within the field of learning and memory.

7. Guanylate cyclases: regulation, tissue distribution and participation in neuronal function

GCs are widely distributed signal transduction enzymes involved in a variety of cellular processes including host defense reactions, cell growth and cell proliferation (for a review see Evgenov et al., 2006). In response to various cellular stimuli, they convert GTP into the second messenger cGMP. In contrast to the transmembrane pGC that serves as a receptor for atrial, B-type and C-type natriuretic peptides, sGC is a receptor for gaseous ligands, especially NO. As a result, sGC is especially interesting in relation to brain neuroplasticity and memory formation. It can associate with the plasma membrane through protein-protein interactions in a constitutive or Ca^{2+}-dependent manner (Agullo et al., 2005; Burette et al., 2002; Russwurm et al., 2001; Zabel et al., 2002). sGC is typically found as a heterodimer, consisting of a larger α-subunit and a smaller haem-binding β-subunit, although it also exists as homodimer (Zabel et al., 1999). Four human sGC subunits have been identified: α1, α2, β1 and β2 of which the α1/β1 and α2/β1 dimers are the most well-known (Table 4). The β-subunit contains an evolutionarily conserved amino-terminal haem-binding domain, which is crucial for the sensing of NO. Based on sequence homology with the crystallized catalytic domains of AC, the carboxy-terminal catalytic domains of both sGC subunits are assumed to be orientated in a head-to-tail fashion. The catalytic domains of both subunits are required for the formation of a catalytic active center (Evgenov et al., 2006; Mayer and Koesling, 2001; Winger and Marletta, 2005).

The different human isoforms of sGC have been known for some time, however little is known about their overall tissue distribution (Budworth et al., 1999). Studies of rat brain have located sGC mRNA predominantly in striatum, the olfactory system and layers II and III of the cerebral cortex (Ding et al., 2004). More recently, expression patterns in human brain and peripheral tissues have been determined. In all the regions of the human brain investigated, pituitary gland and placenta β1 mRNA expression is greater than α1 (Budworth et al., 1999). Most of the other tissues studied showed greater α1 expression compared to β1 especially in heart, prostate, small intestine and appendix. Some of the tissues displayed very low levels of expression of both subunits including skeletal muscle, bladder, testis and peripheral leukocytes. In contrast to the adult tissue, fetal brain showed similar levels of α1 and β1. Both adult and fetal heart displayed more α1 than β1. Fetal lung showed greater sGC expression than adult lung.

7.1. Role of sGCs in synaptic plasticity and memory

NO/sGC/cGMP signaling can be compromised either by reducing the bioavailability of NO or by altering the redox state of sGC itself, thereby making it unresponsive to endogenous NO and NO-releasing drugs (Evgenov et al., 2006). This led to the development of two drug classes to be able to overcome these obstacles: sGC stimulators (stimulate sGC directly and enhance sensitivity of the reduced enzyme to low levels of bioavailable NO) and sGC activators (activate the NO-unresponsive, haem-oxidized or haem-free enzyme). However, sGC stimulators and activators have mainly been investigated for their potential as treatment of arterial and pulmonary hypertension, heart failure, atherosclerosis, thrombosis, erectile dysfunction, renal fibrosis and failure, and liver cirrhosis. Targeting sGC to enhance multiple aspects of memory processes in particular or neuroplasticity in general, is a relatively new strategy in the field of sGC drug development, hence, the limited availability of literature. To investigate the potential of enhanced sGC signaling to improve memory function, studies use, next to stimulators and activators, GC inhibitors as negative control. In this respect, ODQ, a GC inhibitor (Garthwaite et al., 1995), has shown to impair memory performance during the novel object recognition (NOR) test in mice when administered 30 min before the retention trial (Akar et al., 2014). Furthermore, ODQ impaired performance on the passive avoidance test when administered 30 min before acquisition, but only when combined with the NO precursor 7-nitroindazol (7-NI). By itself neither drug had an effect. ODQ also significantly impaired olfactory memory as reflected by the decreased ratio ‘percent cued food/percent total food eaten’ in the social transmission of food preference test when compared to the control group. ODQ has also shown to suppress LTP in several studies (e.g. Arancio et al., 1995; Boulton et al., 1995; Chien et al., 2003; Zhuo et al., 1994. Similarly, bilateral intrahippocampal administration of the sGC inhibitor LY 83,583 caused full amnesia for inhibitory avoidance when given immediately after training, but not 30 min post-training Bernabeu et al., 1997b).

Alternatively, the compound YC-1 which activates as well as stimulates sGC, was shown to significantly decrease the acquisition latency (1–4 days) of 24-month-old rats in the MWM when administered daily for 2 weeks (Komsuoglu Celikyurt et al., 2014). Additionally, the same 24-month-old rats showed a reduced time spent in the escape platform's quadrant when compared to 4-month-old rats. YC-1 reversed the reduction of the time spent in the escape platform's quadrant of the 24-month-old rats. YC-1 also reversed the diminished retention latency in 24-month-old rats on the second day during the passive avoidance task.

Additional support comes from Chien and colleagues, who also showed that YC-1 shortened the escape latency in the MWM during the test trial when injected 10 min before the first trial of each daily

Table 4
Summary of the different types of guanylate cyclases, their tissue-specific distribution and function in the brain. GC = guanylate cyclase, NO = nitric oxide.

Type	Subunit	Expression	CNS function
Membrane-bound GC	n.a.	pineal gland, cerebellum, pituitary, olfactory epithelium	receptor for atrial, B-type and C-type natriuretic peptides
Soluble GC	α1, α2, β1, β2	Heart, prostate, small intestine, appendix, Pituitary gland, placenta, hippocampus, striatum, cerebral cortex and locus	receptor for gaseous ligands, especially NO

Table 5
Summary of the different types of protein kinase G, their tissue/region-specific expression and function in the brain. PKG = protein kinase G.

Type	Group	PKG Isoform	Expression	CNS function
Soluble PKG	PKGI	PKGIα	Cerebellum, dorsal root ganglia, lung	Diverse, including memory
		PKGIβ	Hippocampus, olfactory bulb, smooth muscle, platelets	Diverse, including memory
Membrane-bound PKG	PKGII	n.a.	thalamus, septum, amygdala, olfactory bulb, intestinal mucosa, kidney, chondrocytes	Scarce investigation into neuronal function

training session, and increased and decreased the retention scores in the passive and active avoidance task, respectively, when injected 10 min before foot-shock training. Administration of YC-1 30 min after foot-shock stimulation did not significantly affect retention scores in response to the passive avoidance task. Administration of scopolamine, a cholinergic muscarinic antagonist, markedly impaired memory acquisition. Pretreatment with YC-1 inhibited the scopolamine-induced learning deficit. The enhancement of learning behavior by YC-1 was antagonized by ICV injection of the NOS inhibitor L-NAME and PKG inhibitors KT5823 and Rp-8-Br-PET-cGMPS, indicating that the NO/cGMP/PKG pathway is involved in the action of YC-1 (Chien et al., 2008, 2005).

8. Role of PKG in synaptic plasticity and memory

PKG exists in two forms, the soluble PKGI and the membrane-bound PKGII (Hofmann, 2005; Schlossmann and Hofmann, 2005). The two PKG families (PKGI and PKGII) are encoded by different genes and they are both homodimers consisting of two identical subunits, the C and the R (Table 5). Each subunit has two binding sites for cGMP at the R domain, and allosteric binding of cGMP increases the catalytic kinase activity of the enzyme 3- to 10- fold. Binding of cGMP to the R site does not lead to its dissociation from the C site.Two isoforms of PKGI exist, PKGIα and PKGIβ, which differ in their N-terminal domains. PKGIα is activated at 10-fold lower cGMP concentrations compared to PKGIβ. Both exhibit different physiological functions because they interact with different substrates, vary in their regional and subcellular localization, and are expressed in different tissues. PKGIα is highly expressed in cerebellum, dorsal root ganglia and lung, whereas PKGIβ is found predominantly in hippocampus, olfactory bulb, smooth muscle and platelets. PKGIβ expressed in the hippocampus is therefore believed to be involved in LTP and spatial learning and memory. Interestingly, PKGI KO mice showed no deficits in spatial and fear contextual memory, while LTP impairment was present in old, but not young mice, after a repetitive theta-burst stimulation protocol. Considering that LTP induced by the implemented protocol requires protein synthesis, the authors suggested that PKGI in hippocampus is involved in synthesis-dependent L-LTP (Kleppisch et al., 2003).

Hippocampal PKGI signaling has shown to be mediated by vesicle trafficking regulated by RhoA and vasodilator-stimulated phosphoprotein (VASP) (Wang et al., 2005b). PKGII is localized at the plasma membrane and is expressed in the thalamus, septum, amygdala and olfactory bulb, as well as intestinal mucosa, kidney and chondrocytes. PKGII is much less investigated in relation to neuronal functions including learning and memory, although PKGII KO mice have shown to exhibit significant deficits in spatial learning in the MWM (Wincott et al., 2013).

The critical role of PKG in especially the early stages of memory function was suggested by studies using PKG activators and PKG inhibitors (which do not differentiate between PKGI and PKGII). First support for a role of PKG in memory formation comes from the finding that PKG inhibitors block LTP, and PKG activators facilitate LTP in response to weak tetanic stimuli (e.g. Arancio et al., 2001, 1995; Izquierdo et al., 2000; Zhuo et al., 1994). Also, rats submitted to memory paradigms showed a significant increase in PKG activity in the hippocampus (e.g. Bernabeu et al., 1997b). Interestingly, the increase in PKG was only observed immediately after training, whereas no changes were observed 30 min after training raising the idea that the hippocampal PKG cascade is involved in the early stages of memory formation. This is supported by the observation that the PKG activator 8-Br-cGMP showed a dose-dependent improvement in object recognition compared to saline condition, when administered bilaterally into the hippocampus of rats immediately after the learning trial in the ORT (Prickaerts et al., 2002a). Similarly, intrahippocampal infusions of the PKG inhibitor KT5823 reversed an amyloid-β (Aβ)-induced increase in escape latency and traveled distance in the MWM (Shariatpanahi et al., 2016).

9. Regulation of the intracellular concentration of cyclic nucleotides

The intracellular levels of cyclic nucleotides mainly depend on the fine-tuning between their rate of production by AC and sGC and the rate of elimination. The latter is mainly achieved by PDEs and by energy-dependent transport of cyclic nucleotides to the extracellular space. Additionally, the intracellular concentration of cyclic nucleotides is regulated by their sequestration into functionally distinct compartments within the cell.

9.1. Energy-dependent transport of cyclic nucleotides

The concept of active transport of cyclic nucleotides into the extracellular space has been mainly studied in other tissues rather than the brain. Transport of cyclic nucleotides involves an organic anion transport process that utilizes multidrug resistant proteins (MRPs). Although there is scarce of evidence regarding the exact function of all the members of the MRP family, it has been shown that cyclic nucleotides can be substrates for MRP4, 5 and 8 (Chen et al., 2001; Guo et al., 2003; Jedlitschky et al., 2000; Liqi and Theresa, 2002). Although both cyclic nucleotides were shown to be substrates for these three MRP subfamilies, a later study conducted with human erythrocytes suggested that MRP5 mediates cGMP transport 20-times more efficiently than transport for cAMP, indicating that cGMP is a more favorable substrate for MRP5. Along the same lines, it was also shown that the cGMP-specific PDE inhibitor, sildenafil, can block MRP5-mediated export of cGMP (Jedlitschky et al., 2000).

Regarding the expression of MRP1-6 in the adult human brain, it was shown that only MRP1, 4, 5 are present in the brain, while the other members of the family are not detectable in brain tissue (Nies et al., 2004). Interestingly, MRP4 and 5 were both detected in astrocytes, while MRP5 was also present in pyramidal cells (Nies et al., 2004). Although MRPs seem to participate in the regulation of cyclic nucleotide concentration in neurons, this observation raises the question of the purpose of an energy-dependent transport of cyclic nucleotides into the extracellular space. A possible explanation could be that this mechanism could serve as a cell-cell communication. For example, in bacteria, cAMP at the extracellular space could bind to membrane receptors and promote their differentiation (Janssens and Van Haastert, 1987). Nevertheless, there is not a mechanism described in mammals that would explain this theory, especially considering that MRP-

mediated transport is unidirectional.

The most prominent explanation is that MRPs facilitate the extracellular transport of cyclic nucleotides where they act as extracellular messengers promoting an autocrine and paracrine mechanism. The concept of extracellular cAMP and cGMP activity is not new (Stone and John, 1990) and it is thought to contribute to plasticity and memory-related functions of cyclic nucleotides (Ricciarelli and Fedele, 2018). In particular, it was shown that upon extrusion to the extracellular space, cAMP is converted to adenosine that subsequently mediates several functions throughout the body and the brain via the adenosine receptors A_1, A_{2A}, A_{2B}, and A_3 (Godinho et al., 2015). More recent evidence showed that externally applied cGMP could improve spatial memory. Specifically, the study of Cabrera-Pastor et al. showed that extracellular cGMP modulates glycine receptors leading to an increase in intracellular Ca^{2+} and subsequently CaMKII activation (Cabrera-Pastor et al., 2016).

9.2. Degradation of cyclic nucleotides by PDEs

Regulation of intracellular concentration of cyclic nucleotides through degradation by PDEs has been extensively studied. By hydrolyzing cAMP and cGMP, PDEs play an important role in regulating signal transduction mediated by cyclic nucleotides (Beavo, 1995). PDEs are grouped into 11 families based on homology of the catalytic domain. Most of the families have more than one gene and each gene can consist of several different splice variants and isoforms (Bender and Beavo, 2006). In total, there are estimated to be over 100 specific human PDEs, discretely localized to specific subcellular domains (Houslay, 2010; Keravis and Lugnier, 2012). Additionally, the different families of PDEs differ in their tissue distribution, properties and substrate specificity with the latter constituting a fundamental distinction between the PDE families. PDE1, PDE2, PDE3, PDE10, PDE11 have a dual substrate specificity, hydrolyzing both cAMP and cGMP. PDE4, PDE7 and PDE8 are cAMP-specific, while PDE5, PDE6 and PDE9 are cGMP-specific (Table 6). Except for their role in hydrolysis, PDEs mediate a more complex role in regulating and refining cyclic nucleotide signaling in the brain. In this respect, it was shown that cyclic nucleotides can regulate the activity of PDEs, providing a point of crosstalk in which cAMP signaling could influence cGMP signaling and vice versa (Fig. 1).

With the exception of PDE6 that is mainly found in the retina, all the other families are expressed in several brain areas including the hippocampus. Thereafter, several studies investigated the potential of PDE inhibitors as cognitive enhancers. In the section below the 10 families of PDEs are described and a review is provided on the current studies regarding the role of PDE inhibitors in memory and memory-related diseases.

9.2.1. Dual substrate specificity phosphodiesterases

PDE1 is a unique PDE family that is regulated by Ca^{2+} and activated by calmodulin. Three genes have been identified for the PDE1 family: PDE1A, PDE1B and PDE1C. All three are abundantly expressed in the brain with the highest levels found in the striatum and moderate levels in the cortex and the hippocampus (Cho et al., 2000; Yan et al., 1994, 1996). The kinetic properties for the 3 isoenzymes differ with PDE1A and PDE1B hydrolyzing cGMP with a Km value lower (3 μM) than cAMP (50–100 μM), whereas PDE1C hydrolyzes both cAMP and cGMP with similar Km value (1 μM) (Beavo and Houslay, 1990; Loughney et al., 1996). Interestingly, the affinity of PDE1 for the Ca^{2+}/calmodulin complex is altered by phosphorylation. Specifically, phosphorylation of PDE1A1 and PDE1A2 by PKA (Sonnenburg et al., 1995), and PDE1B1 by CaMKII (Hashimoto et al., 1989), decreases their affinity for Ca^{2+}/calmodulin, resulting in decreased activity for PDE1. Due to its regulation mechanism, PDE1 constitutes an interesting point of crosstalk and integration of intracellular pathways that are mediated by cAMP and cGMP, and pathways that lead to increased Ca^{2+}. In terms of

Table 6
Overview of the different types of phosphodiesterases, their regulation, substrate specificity and tissue-specific expression. CaM = calmodulin, cAMP = cyclic adenosine monophosphate, cGMP = cyclic guanosine monophosphate, PDE = phosphodiesterase.

Type	Genes	Regulation	Substrate	Localization in Body	Localization in the Brain
PDE1	A, B, C	Ca^{2+}-CaM-stimulated	cAMP/cGMP	Heart, smooth muscles, lungs, pancreas, kidneys, bladder, testes	Hippocampus, cortex, olfactory bulb, striatum (highest expression levels), thalamus, amygdala, cerebellum; Expression levels are in general highest for 1A and lowest for 1C
PDE2	A	cGMP-stimulated	cAMP/cGMP	Heart, liver, spleen, pancreas, adrenals, skeletal muscles, bladder, platelets	Hippocampus, cortex, striatum, hypothalamus, amygdala, midbrain
PDE3	A, B	cGMP-inhibited	cAMP/cGMP	Heart, smooth muscles, lungs, liver, pancreas, kidneys, platelets	Throughout the brain low expression levels
PDE4	A, B, C, D	cAMP-specific	cAMP	Wide variety of tissues: e.g., smooth muscles, skeletal muscles, lungs, liver, spleen, pancreas, kidneys, bladder, testes	Hippocampus, cortex, olfactory bulb, striatum, thalamus, hypothalamus, amygdala, midbrain, cerebellum; Expression levels are in general highest for 4B and lowest for 4C
PDE5	A	cGMP-specific	cGMP	Smooth muscles, skeletal muscles, lungs, pancreas, kidneys, bladder, platelets	Hippocampus, cortex, cerebellum
PDE6	A, B, C	Photoreceptor	cGMP	Rod and cone cells in retina	Pineal gland
PDE7	A, B	cAMP high affinity	cAMP	Heart, skeletal muscles, liver, pancreas, kidneys, testes	Hippocampus, cortex, olfactory bulb, striatum, thalamus, hypothalamus, midbrain; Expression levels are in general highest for 7B
PDE8	A, B	cAMP high affinity	cAMP	Heart, liver, pancreas, kidneys, adrenals, lungs, testes, thyroid	Hippocampus, cortex, olfactory bulb, striatum, thalamus, hypothalamus, midbrain; Expression levels are in general highest for 8B
PDE9	A	cGMP high affinity	cGMP	Lungs, spleen, pancreas, kidneys, bladder, prostate, various gastrointestinal tissues	Hippocampus, cortex, olfactory bulb, striatum, thalamus, hypothalamus, amygdala, midbrain, cerebellum
PDE10	A	cAMP-inhibited	cAMP/cGMP	Heart, skeletal muscles, lungs, liver, pancreas, kidneys, testes, thyroid	Hippocampus, cortex, striatum (highest expression levels), midbrain, cerebellum
PDE11	A	Dual substrate	cAMP/cGMP	Skeletal muscles, liver, pancreas, kidneys, testes, prostate, thyroid	Throughout the brain low expression levels

plasticity, the fact that phosphorylation by PKA decreases the activity of PDE1A1 and PDE1A2 indicates that a signal that increases cAMP would further prolong its action, imposing a paradigm of positive feedback that is reversed after increased Ca^{2+} (Beavo, 1995). Additionally, it is reported that cGMP can inhibit PDE1-induced hydrolysis of cAMP (Loughney et al., 1996). Although PDE1 activity significantly contributes to cGMP-mediated inhibition of cAMP hydrolysis in human myocardium, this relationship is not yet determined in neuronal cells. Regarding the action of PDE1 inhibition in the brain, a recent study from Snyder et al. showed that acute treatment with the selective PDE1 inhibitor ITI-214 can improve several stages of mnemonic process in heathy rats after acute treatment (Snyder et al., 2016).

PDE2 is highly expressed in the brain and alternative splicing of the same gene results in 3 isoforms: PDE2A1, PDE2A2 and PDE2A3 (Rosman et al., 1997; Sonnenburg et al., 1991; Yang et al., 1994). In the rat brain, PDE2 mRNA can be found in the hippocampus, cortex, amygdala, cerebellum, striatum and hypothalamus (Stephenson et al., 2012; Van Staveren et al., 2003). The different isoforms of PDE2 differ in their N-terminal sequence introducing differences in their hydrophobicity and subsequently cellular distribution. Additionally, the N-terminus has two cGMP-binding domains, GAF-A and GAF-B, participating in dimerization and binding of cGMP, respectively (Martinez et al., 2002b). Although, PDE2 has a dual substrate specificity, hydrolyzing both cAMP and cGMP with similar catalytic properties (Km = 30 μM for cAMP and 10 μM for cAMP), cGMP seems to be a preferred allosteric modulator for PDE2, causing cGMP to be more effective in activating PDE2 (Beavo et al., 2006). Specifically, binding of cGMP to one of the GAF domains induces an allosteric modification that lowers the Km for cAMP and promotes up to a 30-fold increase in cAMP hydrolysis (Martinez et al., 2002a; Michie et al., 1996). Because of its function, PDE2 is part of a negative feedback mechanism that facilitates crosstalk between cGMP and cAMP pathways, implicating important physiological functions. For example, in the brain, signals that elevate intracellular cGMP levels promote PDE2-mediated cAMP hydrolysis, restoring basal levels of cyclic nucleotides (Bender and Beavo, 2006). Particularly, at the presynaptic terminal of the CA1 area in the rat hippocampus, PDE2A can modulate cAMP levels in response to activation by cGMP, indicating a modulatory role of PDE2A in short-term synaptic plasticity (Fernández-Fernández et al., 2015). The latter was also highlighted in the study of Boyken et al. in which PDE2A expression appeared very high in the docked fraction of synaptosomes, suggesting an important role of PDE2A in neurotransmitter release from the presynaptic terminal (Boyken et al., 2013).

The expression of PDE2 in brain areas that are involved in memory and cognition rendered it a promising target for the development of cognitive-enhancing drugs. The first available PDE2 inhibitor BAY 60–7550 was shown to enhance memory acquisition and consolidation in healthy mice and rats in the ORT when administered before and after the learning trial, respectively (Boess et al., 2004; Rutten et al., 2007). These memory enhancing effects of BAY 60–7550 are inhibited after co-administration of NOS or PKG inhibitors, indicating that the effect of BAY 60–7550 on memory seems to be mediated primarily through activation of the sGC/cGMP/PKG cascade (Domek-Łopacińska and Strosznajder, 2008). Additionally, it was shown that BAY 60–7550 could improve memory performance in a mouse model for AD, without combating the Aβ pathology of the disease (Sierksma et al., 2013).

PDE3 is encoded by two genes, PDE3A and PDE3B with three (PDE3A1, PDE3A2,PDE3A3) (Wechsler et al., 2002) and one splice variants (PDE3B1) (Beavo et al., 2006), respectively. In the rat brain, PDE3A mRNA has been found in the cortex, cerebellum and brain stem (Bolger et al., 1994), while PDE3B mRNA is mainly found in peripheral tissues with prominent expression in the cardiovascular system (Reinhardt et al., 1995). PDE3 hydrolyzes both cAMP and cGMP in a competitive manner, with same catalytic properties for both nucleotides (Km = 0.2 μM for cAMP and Km = 0.1 μM for cGMP). However, the velocity for cAMP hydrolysis is 4- to 10-fold higher than for cGMP and the substrate affinity for cGMP is higher (Beavo, 1995). Therefore, increased production of cGMP through activation of sGC, could inhibit PDE3-mediated hydrolysis of cAMP, rendering it a cGMP-inhibited PDE.

The different variants are distinguished by the different lengths of the N-terminal domain. The difference in length of the N-terminus between the variants determines their subcellular localization and their regulation by kinases. The longest variant, PDE3A1, has two N-terminal hydrophobic associated regions (NHR1 and NHR2). It also contains one phosphorylation site for protein kinase B (PKB) and two phosphorylation sites for PKA. The latter was shown to activate PDE3A1 (Wechsler et al., 2002), downregulating cAMP signaling through negative feedback. PDE3A2 lacks the NHR1 domain along with the PKB phosphorylation site, but contains NHR2 and the two phosphorylation sites for PKA. The shortest variant, PDE3A3, lacks all the above domains and phosphorylation sites (Zaccolo and Movsesian, 2007).

There are several drugs that can inhibit both isoenzymes equally including cilostazol, cilostamide, enoximone and milrinone. Considering the role of PDE3 inhibitors in memory and cognition enhancement, most of the supportive evidence comes from studies conducted with cilostazol. Behavioral studies showed that the neuroprotective effect of cilostazol against Aβ-induced memory impairments can, at least in part, be attributed to reduction of oxidative stress and prevention of Aβ accumulation (Hiramatsu et al., 2010; Park et al., 2011). A study conducted with a transgenic mouse strain that exhibits accelerating aging showed that administration of cilostazol for 3 months could have a neuroprotective effect that is reflected in the molecular level by increased p-CREB in the hippocampus and improved integrity of the blood-brain barrier (BBB) (Yanai et al., 2017). Finally, it was shown that treatment with cilostazol for one month could protect against tau pathology and cognitive decline in the rTg4510 mouse line via increasing proteasome activity (Schaler and Myeku, 2018).

PDE10 and PDE11 are two distinct families that were characterized more recently. Regarding **PDE10**, the entire family is encoded by one gene, PDE10A, and alternative splicing generates 18 splice variants (PDE10A1-18) (Strick et al., 2006). In rat brain, PDE10A mRNA is highly expressed in the striatum, but it is also found in the hippocampus, cortex and cerebellum (54, 56, 57). PDE10A hydrolyzes both cyclic nucleotides with a significantly higher affinity for cAMP (Km = 0.20 μM) than for cGMP (Km = 1 μM). Because the maximum velocity for hydrolyzing cGMP is 5-fold higher than the one for cAMP, PDE10A hydrolysis of cGMP seems to be inhibited by cAMP (Fujishige et al., 1999; Soderling et al., 1999). Therefore, PDE10A may function as a cAMP-inhibited phosphodiesterase and as a result, stimuli that elevate cAMP could subsequently increase cGMP levels. This function is opposite from the one described for the PDE3 family (Bender and Beavo, 2006). As with PDE2, PDE10A has 2 GAF domains in the N-terminus. *in vitro* studies have shown that the GAF domains of PDE10A have very low affinity for cGMP (Soderling et al., 1999), and it is considered highly impossible for a cell to reach such high concentrations of cGMP in order to bind to each one of the GAF domains. Nevertheless, the possibility that a certain regulation could increase the affinity of GAF domains for cGMP cannot be abolished. Accordingly, it was recently shown *in vitro* that PDE10A allosterically binds cAMP in one of the GAF domains (Gross-Langenhoff et al., 2006). Regarding its function in the hippocampus, it was reported that mRNA levels of specific PDE10A splice variants are increased after induction of LTP, providing a regulatory mechanism to dampen LTP-induced elevated levels of cGMP (O'Connor et al., 2004).

PDE10A1 and PDE10A2 represent the major PDE10A variants in humans (Fujishige et al., 1999, 2000). A notable difference between the two isoforms is that only PDE10A2 has a PKA phosphorylation site at the N-terminal domain (Kotera et al., 1999b) that alters its localization from Golgi apparatus to cytosol (Kotera et al., 2004). That change in PDE10A2 distribution may represent a negative feedback in response to elevated cytosolic levels of cAMP (Kotera et al., 2004). In concordance

with the abundant expression of PDE10A in the striatum, development of PDE10 inhibitors currently aims at the treatment of motor disorders. In addition, PDE10 inhibition was shown to have antipsychotic potential and improved cognitive symptoms in animal models of schizophrenia, providing a new therapeutic approach for the disorder (Grauer et al., 2009; Megens et al., 2014; Menniti et al., 2007; Schmidt et al., 2008), though clinical trials with schizophrenia patients did not results in any positive effects.

PDE11 is the newest member of the PDE family which has similar affinities for both nucleotides (Km = 1–2 μM for cGMP and Km = 2–3 μM for cAMP), and catalyzes both substrates with similar velocity. Four splice variants of the PDE11A gene have been identified (PDE11A1-PDE11A4) that differ in the amino-terminal sequence. PDE11A2 and PDE11A3 have one complete and one incomplete GAF domain in the N-terminus (Beavo et al., 2006), whereas PDE11A4 has two complete GAF domains with phosphorylation sites for PKA and PKG (Yuasa et al., 2000). Expression of PDE11 in the brain is relatively low, but it is profoundly distributed in the ventral hippocampus, CA1, subiculum and the amygdalohippocampal area (Kelly et al., 2010). Nevertheless, there is a recent study showing that PDE11 KO mice exhibit particular behavioral and biochemical changes observed in psychiatric disorders including hyperactivity and deficits in tests related to social behavior (Kelly et al., 2010). The involvement of PDE11 in social memory came from a later study in which PDE11 KO mice exhibited normal STM, but not LTM, for social recognition, while non-social odor recognition memory was unaffected. The impaired consolidation of social memory was shown to be associated with decreased protein synthesis in the ventral hippocampus (Hegde et al., 2016a, b). Recently, the first potent PDE11 inhibitors have been identified in a high-throughput screen in a yeast-based assay, paving the way for the development of selective PDE11 inhibitors (Ceyhan et al., 2012).

9.2.2. cAMP-specific phosphodiesterases

This category of PDEs contains three members that are all highly expressed in the brain; PDE4, PDE7 and PDE8. Among them, **PDE4** has a prominent position since it is the best characterized and inhibition of PDE4 constitutes a potent method for upregulating the cAMP/PKA (Km < 10 μM) cascade. Additionally, PDE4 enzymes are distinguished from other PDEs due to their specific inhibition by rolipram. PDE4 is encoded by four different genes (PDE4A-PDE4D), and more than 25 different human isoforms have been described (Beavo et al., 2006). PDE4A, PDE4B and PDE4D are highly expressed in the hippocampus, striatum, thalamus, cortex and cerebellum, while the expression of PDE4C in the brain is relatively low (Lakics et al., 2010). PDE4A and PDE4B constitute the majority of membrane-bound PDE4, and PDE4D the majority of soluble PDE4 in the brain (McPhee et al., 1995).

PDE4 enzymes have two unique highly conservatory domains at the N-terminal domain; upstream conserved region 1 and 2 (UCR1 and UCR2). The presence or absence of these domains divides PDE4 isoforms into three groups: the long, the short and the super short variants. Specifically, the long variants have both the UCR1 and UCR2 domains, the short variants have a complete UCR2 domain and the super-short variants have a truncated UCR2 domain (Bolger et al., 1993). UCR1 has a phosphorylation site for PKA and upon phosphorylation diminishes PKA's affinity to UCR2, and subsequently promotes PDE4 activation (Beard et al., 2000). Furthermore, PKA phosphorylation alters the sensitivity of PDE4 towards inhibition by rolipram (HOFFMANN et al., 1998), probably due to conformational changes in the catalytic region (Beard et al., 2000). The activity of PDE4 is also regulated by ERK phosphorylation in the catalytic domain. ERK phosphorylation promotes activation of the short PDE4 variants and inhibits the long PDE4 variants, while the ERK phosphorylation motif is absent in the super short variants (Baillie et al., 2000). Therefore, phosphorylation by ERK and PKA is particularly interesting in the case of long isoforms and is considered to regulate cAMP signaling. Activation of ERK can inhibit the activity of the enzyme, elevating cAMP levels. Subsequently, PKA activation reliefs ERK-mediated inhibition and reactivates catalytic activity of PDE4, lowering cAMP to its basic levels (Hoffmann et al., 1999). Although it is not shown yet in neuronal cells, CaMKII can also modulate PDE4D activity in cardiac myocytes. At both basal state and after stimulation of the cAMP pathway, CaMKII activates PDE4D via phosphorylation providing an additional mechanism, besides PKA-mediated PDE4 activation, for controlling intracellular cAMP levels (Mika et al., 2015).

Crystallographic studies revealed multiple conformations for PDE4 isoenzymes that could also alter the catalytic activity of the enzyme (Burgin et al., 2010). In one conformation, the α-helix-UCR2 from one monomer folds over and interacts with the catalytic site of the other monomer, resulting in > 50 % inhibition of the enzyme. The UCR2 autoinhibition is removed by PKA phosphorylation of UCR1. Conversely, phosphorylation by ERK stabilizes the UCR2-autoinhibition state (Houslay and Adams, 2010). The sequence of the α-helix is the same for all the isoforms with the exception of a single amino acid that differentiates PDE4D from the other PDE4 isoforms. In fact, this polymorphism has been utilized for the development of isoform-selective inhibitors (Burgin et al., 2010; Houslay and Adams, 2010). In a different PDE4 conformation, the helix of the C-terminus, which is called Control Region 3 (CR3), interacts with the catalytic site of the same monomer, causing complete autoinhibition of the enzyme. As with UCR2, a unique polymorphism in the CR3 helix distinguishes PDE4B and PDE4D isoforms and has been exploited for the development of selective PDE4B inhibitors with promising anti-inflammatory action (Ahmad et al., 2015; Fox et al., 2014).

Since PDE4 is highly expressed in the hippocampus, PDE4 inhibitors have been extensively studied as cognitive enhancers. In addition to pro-cognitive action, rolipram was shown to reverse plasticity impairments and cognitive decline in several transgenic AD mouse models (Barad et al., 1998; Costa et al., 2007; Gong et al., 2004; Rutten et al., 2006). The cognitive enhancing effect of rolipram was related to the attenuation of decreased CREB phosphorylation, as observed in the disease (Yamamoto-Sasaki et al., 1999). In the study of Vitolo et al. it was suggested that the Aβ peptide prevents AC activation leading to lower intracellular levels of cAMP that shifts the equilibrium towards the inactive form of PKA. Subsequently, treatment with rolipram restores the balance, promoting PKA dissociation and CREB phosphorylation (Vitolo et al., 2002). Except for restoring CREB phosphorylation, it was shown that activation of cAMP/PKA can enhance proteasome activity and subsequently promote tau clearance (Myeku et al., 2016). Similarly, a newly synthetized PDE4 inhibitor FFPM was also shown to ameliorate cognitive decline in APP/PS1 mouse model by promoting cAMP/PKA/p-CREB/BDNF pathway and reducing the levels of inflammatory factors (Guo et al., 2017). Another possible mechanism by which PDE4 inhibition could be neuroprotective against AD pathology is via activation of the small heat-shock protein 20 (Hsp20). In particular, Hsp20 binds directly to PDE4 within a region of the catalytic domain, remaining in a non-phosphorylated state (Sin et al., 2011). Disruption of Hsp20-PDE4 complex for example via PDE4 inhibition promotes phosphorylation of Hsp20 by PKA/PKG at Ser16. Subsequently, phosphorylated Hsp20 interacts with Aβ preventing its aggregation into toxic oligomers (Cameron et al., 2014). Although the latter finding suggests that PDE4 inhibition could protect against Aβ pathology, there is no animal study at the moment showing that PDE4 inhibition could combat amyloid deposition.

Despite the promising preclinical findings, clinical studies with PDE4 inhibitors have been hampered due to dose-limiting emetic effects. In this respect, recent studies indicate the importance of developing more selective PDE4 inhibitors in order to dissociate the pro-cognitive action from the emetic effect. The newly described PDE4 inhibitors GEBR-7b and GEBR-32a enhanced memory performance in healthy mice and an AD mouse model with doses being at least 100 times lower than the one inducing emesis (Bruno et al., 2011; Ricciarelli et al., 2017). Of note, it was shown that the cognitive enhancing effect

of GEBR-7b does not involve changes in Aβ pathology (Bruno et al., 2011). Roflumilast, a PDE4 inhibitor that is already clinically approved for the treatment of chronic obstructive pulmonary disease (COPD) (Hatzelmann et al., 2010), was shown to improve cognition in both healthy adult rodents as well as healthy adult volunteers at non-emetic doses (Van Duinen et al., 2018; Vanmierlo et al., 2016). Finally, development of allosteric modulators of PDE4 gained more interest the past few years. Accordingly, the allosteric modulator D159687 was shown to exert pro-cognitive action in cynomolgus macaques, at a dose that is 60 times lower than the one eliciting emesis (Burgin et al., 2010).

When it comes to treatment with PDE4 inhibitors or other drugs that upregulate cAMP signaling, an important aspect is the transcriptional regulation of the PDE4 family by cAMP. Several studies have shown that chronic treatment with antidepressants that stimulate the cAMP signaling pathway, could upregulate expression of PDE4A and PDE4B in the rat frontal cortex without affecting PDE4D levels (Takahashi et al., 1999; Ye et al., 1997). Later studies that examined in more detail the expression of the different variants of PDE4A, PDE4B and PDE4D isoforms after chronic administration of fluoxetine showed a more complex regulation of their expression (Dlaboga et al., 2006). Repeated treatment with fluoxetine increased PDE4D1/PDE4D5 in the mouse cerebral cortex, while it decreased expression of all the PDE4B variants tested. Additionally, PDE4D3 expression was increased in both the cerebral cortex and the hippocampus (Dlaboga et al., 2006). Further studies showed that fluoxetine administration reduced PDE4D3 expression in the cingulate cortex, while PDE4D4 expression was increased in the frontal and frontoparietal cortex. Moreover, expression of PDE4D1 and PDE4D5 was decreased in several areas of the hippocampus (Miró et al., 2002). These studies indicate that the earlier results, showing unaltered levels of PDE4D expression after fluoxetine treatment, most likely represent the net result of opposing changes in different PDE4D splice variants. In cortical cell cultures, stimulation of cAMP by dibutyryl-cAMP promotes the expression of the short variants PDE4B2 and PDE4D1/PDE4D2, while PDE4A levels remain unaltered. This finding is particularly interesting since these variants were almost undetectable at basal conditions, and their expression was increased in a cAMP-activated state (D'sa et al., 2002). Additionally, repeated treatment with rolipram differentially altered the expression of the PDE4 variants in the cerebral cortex and the hippocampus. PDE4D3 expression was increased in both brain areas examined. Nevertheless, chronic treatment with rolipram decreased PDE4A1/PDE4A5 levels in the hippocampus, while PDE4B1/PDE4B2/PDE4B3 expression was increased in the cerebral cortex. Taken together, all the above mentioned studies indicate that transcription of PDE4 variants in the brain is controlled by cAMP signaling in a isoenzyme and brain-specific manner (Sasaki et al., 2004).

The **PDE7** family includes two genes, PDE7A and PDE7B, and hydrolyses cAMP with high affinity (Km < 0.2 μM). Alternative splicing gives rise to three splice variants for PDE7A (PDE7A1-3) (Glavas et al., 2001; Han et al., 1997) and PDE7B (PDE7B1-3) (Sasaki et al., 2000) in rats. However, in humans only one variant has been described for PDE7B. Although the N-terminal domain does not contain regulatory sites, it interacts directly with the catalytic domain of PKA, inhibiting its action (Han et al., 2006). The latter provides an alternative way in which PDE7 could downregulate the cAMP/PKA signaling pathway. Due to the high expression of PDE7A1 and PDE7A3 in a variety of human immune cells, specific inhibition of these variants seems a promising approach for preventing chronic inflammation (Glavas et al., 2001; Smith et al., 2003). Except for peripheral tissues, PDE7 is highly expressed in the brain and both PDE7A and PDE7B were found in the hippocampus, cortex and striatum in the rat brain (Johansson et al., 2012; Miro et al., 2001). PDE7B1 is ubiquitously expressed in the striatum and it was shown to possess a prominent role in regulating dopamine-mediated cAMP signaling in striatal neurons (Sasaki et al., 2004). Elevation of cAMP/PKA levels in the striatum promotes transcriptional activation of PDE7B1 providing a negative feedback that eventually down-regulates intracellular cAMP levels (Sasaki et al., 2004). Therefore, development of specific inhibitors for the PDE7B1 isoform could be an alternative strategy for the treatment of diseases related to loss of dopaminergic signaling. Although there are a few potent PDE7 inhibitors, there is a scarce of evidence regarding their effect on memory. A newly described compound VP1.15 that inhibits both PDE7 and glycogen synthase kinase 3 (GSK-3) showed pro-cognitive action in healthy mice (Lipina et al., 2013). Additionally, chronic treatment with the PDE7 inhibitor S14 in AD mice ameliorated memory impairment and reduced pathological hallmarks of the disease, including Aβ deposition and tau phosphorylation (Perez-Gonzalez et al., 2013). Clearance of Aβ deposits was mediated by astroglial phagocytosis, outlining the protective potential of PDE7 inhibition against neuroinflammation.

The **PDE8** family contains two genes, PDE8A and PDE8B, and shows the highest catalytic rates for cAMP (Km ~ 0.8 μM) among all PDEs. PDE8A mRNA is expressed in a variety of peripheral tissues and with regard to its brain expression, it can be found in the substantia nigra, thalamus and to a lesser extend in the hippocampus and cortex (Kruse et al., 2011). PDE8B mRNA is mainly expressed in the brain and more precisely in the hippocampus, cortex, striatum and midbrain (Kobayashi et al., 2003). The N-terminal region contains REC (receiver) and PAS (Per, Arnst and Sim) regulatory domains that participate in a communication system and in protein interaction in prokaryotes. Their specific function in vertebrates remains unknown. Similarly to other PDE families, upon increased cAMP levels, PKA phosphorylation increases the catalytic activity of the enzyme, providing a negative feedback mechanism (Brown et al., 2012). Considering the high distribution of PDE8B in the hippocampus, it is considered a promising target for the treatment of memory-related disorders. To our current knowledge, one selective PDE8B inhibitor has been identified, but preclinical development was halted due to peripheral side effects in dogs (DeNinno et al., 2012).

9.2.3. cGMP-specific phosphodiesterases

This category of PDEs comprises PDE5, PDE6 and PDE9, with PDE5 representing the most well-studied family. **PDE5** is encoded by a single gene with different promoters resulting in three variants of the gene, i.e. PDE5A1, PDE5A2 and PDE5A3. The three variants differ at their N-terminus and tissue localization. Although PDE5 has two GAF domains (GAF-A and GAF-B) at the N-terminus, cGMP binds only to GAF-A. Activation of the enzyme requires a well-orchestrated series of events that is initiated by elevated intracellular cGMP levels. Subsequently, cGMP interacts with the catalytic domain, facilitating binding of cGMP to the GAF-A domain (Francis et al., 1980; Thomas et al., 1990). The latter promotes phosphorylation of specific serine residual that increases by 10-fold the affinity of the enzyme for cGMP and additionally promotes its catalytic activity (Corbin et al., 2000; Francis et al., 2002). The main kinase that mediates this phosphorylation is PKG. Nevertheless, when cGMP reaches high levels, PKA can also phosphorylate the enzyme, prolonging its activation. This mechanism provides a negative feedback loop, ensuring that intracellular cGMP concentration will not exceed the appropriate levels (Corbin et al., 2000). Additionally, both cyclic nucleotides were shown to promote transcriptional regulation of PDE5A via regulatory elements in the promoter of the gene. In rat cell cultures, a cAMP analog stimulated transcription of PDE5A2 and in lesser extend PDE5A1, probably via association with CRE (Kotera et al., 1999a). Additionally, cGMP and cAMP were shown to facilitate PDE5A1 transcription via the AP-2 and Sp-1 sequences in the promoter of the gene (Lin et al., 2001).

Similar to PDE3 and PDE4 inhibitors, PDE5 inhibitors are well-known for their vascular effects. More specifically, PDE5 inhibition causes relaxation of smooth muscles in blood vessels, hence its importance for the treatment of erectile dysfunction. Sildenafil, vardenafil and tadalafil are examples of FDA approved PDE5 inhibitors for the treatment of erectile dysfunction. Because of their vasodilatory

properties, sildenafil and tadalafil are also FDA approved for the treatment of hypertension of the pulmonary artery. Nevertheless, there is an extensive body of evidence indicating their promising cognitive enhancing properties in healthy, aged and AD animal models. Several studies showed that sildenafil improves memory formation in healthy mice, rats and cynomolgus macaque, either when given before or immediately after the mnemonic test (Prickaerts et al., 2005, 2002b; Rutten et al., 2008, 2005). Additionally, sildenafil could compensate against memory impairments in AD and aged mice. In addition to restored CREB phosphorylation, treatment with sildenafil also resulted in reduction of pathological hallmarks related to AD and aging. For example, chronic treatment with sildenafil reduced Aβ deposition in APP/PS1 mice (Puzzo et al., 2009), and normalized the amyloidogenic APP cleavage pathway in aged mice (Puzzo et al., 2014). Accordingly, a recent study showed that as with rolipram, sildenafil could activate Hsp20 in cell cultures, preventing aggregation of toxic Aβ fibrils (Cameron et al., 2017).

Despite the cerebrovascular effect of PDE inhibitor, animal studies showed that the cognitive enhancing properties of sildenafil cannot be attributed to increased cerebral blood flow (Rutten et al., 2009) and metabolism in the brain, but are mainly related to underlying mechanisms of plasticity (Puzzo et al., 2009; Zhang et al., 2013). Nevertheless, four clinical studies have tested the effects of PDE5 inhibition on memory in healthy volunteers and none of these studies proved a therapeutic benefit on cognitive function (Prickaerts et al., 2017). Cognitive ceiling effects may have been a limiting factor in these studies, since they were conducted in healthy volunteers. Another point of concern regarding the commercially available PDE5 inhibitors is their lack of selectivity. For example, sildenafil also inhibits PDE6 that is expressed in the retina and therefore chronic administration could cause visual disturbances. The past few years considerable efforts have been made for the development of more selective PDE5 inhibitors with optimal kinetic properties. In this respect, the newly synthetized compounds 7a and 6c represent optimized versions of the existing PDE5 inhibitors with higher selectivity for the enzyme and increased BBB permeability (Fiorito et al., 2013, 2017). Additionally, both inhibitors were shown to exert neuroprotective mechanism against synaptic and memory deficits in APP/PS1 mice.

PDE9 family is encoded by one gene, PDE9A, and hydrolyses cGMP with the highest affinity (Km ~ 0.17 μM) among the cGMP-specific PDEs, supporting the idea that it is the main regulator of cGMP signaling in the brain (Van Staveren et al., 2002). Despite the identification of one gene, complex processing of its mRNA results in twenty-one splice variants (Rentero et al., 2003). Unlike the other PDEs, the N-terminal domain of the PDE9A isoenzyme does not contain GAF domains or any other regulatory regions. Additionally, the sequence of the catalytic domain appears to be unique among the other PDEs. The latter results in unresponsiveness of PDE9A to common PDE inhibitors (Fisher et al., 1998; Soderling et al., 1998). PDE9A mRNA is expressed in several peripheral tissues. Regarding PDE9A mRNA expression in the brain, studies with rodents showed diverse patterns of distribution of its transcripts, with high levels in the hippocampus, cortex, olfactory bulb, striatum, thalamus, amygdala and the highest expression in the cerebellum (Van Staveren et al., 2002, 2003). At the cellular level, PDE9A is mainly localized in neuronal cell bodies and dendrites (Kleiman et al., 2012). Additionally, PDE9A exhibits a distinct pattern of subcellular distribution that is region-specific. For example, in the cerebellum, PDE9A is evenly distributed in the plasma and nucleus, while in the hippocampus it is mainly found in the nucleus (Patel et al., 2018).

So far, three potent PDE9 inhibitors, BAY 73–6691, PF-04447943 and BI 409306, were shown to promote synaptic plasticity and enhance memory performance in healthy rodents. Additionally, these drugs were able to reverse scopolamine-induced memory impairments in both mice and rats, indicating a promising role for AD (Hutson et al., 2011; Van Der Staay et al., 2008; Vardigan et al., 2011). In that respect, BAY 73–6691 was shown to protect against synaptic deficits induced by $A\beta_{42}$ oligomers and improve memory performance in an AD transgenic mouse model (Kroker et al., 2014). Additionally, it was shown *in vitro* that PDE9 inhibition by either BAY 73–6691 or PF-04447943 could protect against Aβ-induced cytotoxicity (Cameron et al., 2017). The same study showed that PDE9 inhibition offered a higher level of neuroprotection and with an earlier onset in comparison to rolipram and sildenafil treatment (Cameron et al., 2017). Notably, newly synthesized PDE9 inhibitors were able to prevent Aβ aggregation into toxic fibrils and this neuroprotective function was attributed to their antioxidant ability (Zhang et al., 2018) or metal-chelating capacity (Su et al., 2016). Nevertheless, the nuclear distribution of PDE9A suggests that PDE9 inhibition could not compensate for deficits in sGC signaling (Kelly, 2017) that are encountered in both AD patients and models of AD pathology (Baltrons et al., 2002; Bonkale et al., 1995).

10. Signal compartmentalization of cyclic nucleotides

The concept of signal compartmentalization has emerged as a need to understand the complex and specific spatiotemporal signaling processes in response to extracellular stimuli. Since cAMP participates in a plethora of cellular pathways, its signal sequestration is essential for proper regulation. Discrete compartments of cAMP gradients are shaped by A-kinase anchoring proteins (AKAPs) that act as a scaffold, binding several components of the cAMP signaling cascade, including ACs, PDE4, PKA, Epacs and phosphatases. The presence of several components and regulators of the cAMP signaling cascade in the same complex results into feedback loops in which initial activation of ACs and elevation of cAMP levels, activates PKA that eventually potentiates cAMP degradation via PDEs. The AKAP family is comprised of over 50 members (Tasken and Aandahl, 2004; Tröger et al., 2012). Regulation of PKA compartmentalization into discrete intracellular compartments is mainly determined by the subunit composition of PKA. The two R isoforms, RI and RII, and subsequently PKAI and PKAII are differentially expressed in tissues and show distinct cellular distribution. Their interaction with AKAPs mainly contributes to the anchoring of the different PKA classes into specific subcellular structures. Although the majority of AKAPs show preference for the PKAII class (Skroblin et al., 2010), there have been identified AKAPs that are specific for both PKA classes. Considering that the AKAPs anchor together PKA molecules with their substrates or effectors, sequestration of cAMP/PKA signaling provides an advantageous mechanism ensuring fast intracellular responses to extracellular stimuli (for a review, see (Cheng et al., 2008)).

AKAP5, also known as AKAP150 in rodents (orthologue of human AKAP79 and bovine AKAP75), is highly expressed in neural cells and is able to anchor PKAII in the postsynaptic terminal of neurons (Carr et al., 1992; Sarkar et al., 1984). Except for the unique PKA binding domain, AKAP5 also contains three sequences at the N-terminal that facilitate targeting of the anchoring protein to the neuronal plasma membrane. In the mouse brain, AKAP5 is mainly distributed in the hippocampus, amygdala and cortex, suggesting a pivotal role in the processes of learning and memory (Glantz et al., 1992; Moita et al., 2002; Ostroveanu et al., 2007; Ulfig and Setzer, 1999). Regarding its subcellular localization, AKAP5 is found in the dendrites and more specifically in the postsynaptic density (PSD) of dendritic spines, where it regulates their structure and function (Robertson et al., 2009). Tethering of AKAP5 to PSD is achieved via interaction of structural components including PIP2, F-actin, cadherins (Gomez et al., 2002; Gorski et al., 2005) and membrane-associated guanylate kinase (MAGUK) (Colledge et al., 2000; Robertson et al., 2009). In the PSD, AKAP5 interacts with a plethora of signaling molecules including PKC (Faux et al., 1999), calmodulin (Faux and Scott, 1997), CaN (Faux and Scott, 1997), as well as receptors and ion channels including AC5, AC6 (Bauman et al., 2006), L-type calcium channel (Hall et al., 2007; Oliveria et al., 2007), potassium channel (Dart and Leyland, 2001; Tao et al., 2005) and β-adrenergic receptor (Fraser et al., 2000). Additionally, AKAP5 binds indirectly to AMPA receptors via the MAGUK

scaffolding protein SAP-97, and to NMDA receptors via PSD-95 (Colledge et al., 2000), orchestrating glutamatergic neuronal transmission.

Except for the above interaction with structural and signaling molecules, AKAP5 was shown to mediate a well-orchestrated modulation of cAMP pools in neuronal cells via interaction with PDE4. The most well-studied paradigm represents the PKA/AKAP5-mediated regulation of the β2-adrenergic receptor (β2-AR) via PDE4D5 (Houslay, 2010; Lynch et al., 2005). Specifically, β2-AR is coupled to both G_s and G_i proteins and phosphorylation of the receptor by PKA switches its coupling from G_s to G_i (Daaka et al., 1997). Activation of the β2-AR by its agonist promotes activation of AC via G_s that subsequently elevates cAMP intracellular concentration. When this concentration reaches the threshold for promoting activation of AKAP5-anchored PKA, the latter phosphorylates β2-AR and switches its coupling to G_i. The dissociated $G_{\beta\gamma}$ subunit initiates a cascade of signaling molecules that lead to ERK activation (Daaka et al., 1997). Recruitment of the βarrestin-bound PDE4D5 into the β2-AR signaling complex provides a negative feedback by lowering cAMP concentration and attenuating the ability of AKAP5-anchored PKA to phosphorylate β2-AR. In this signaling cascade, disruption of PKA-AKAP5 tethering prevents ERK activation, even when PDE4D5 was knocked-down (Lynch et al., 2005), outlining the importance of sequestration of PKA and PDE4D5 in regulating cAMP concentration.

There is a growing body of evidence indicating that the AKAP5 signalosome is important for mediating neuronal signaling and facilitating mnemonic processes. An example of this action represents the regulation of AMPA receptor trafficking in the synapse. Most of the hippocampal synapses contain GluA1/2 and GluA2/3 AMPA receptors (Kessels et al., 2009). Activation of cAMP signaling increases channel open probability of the GluA3-containing AMPA receptors (Gutierrez-Castellanos et al., 2017; Renner et al., 2017), as well as, trafficking of GluA1-containing AMPA receptors to extrasynaptic sites (Banke et al., 2000; Esteban et al., 2003; He et al., 2009; Man et al., 2007; Oh et al., 2006; Yang et al., 2008). In response to NMDA receptor activation and PKC phosphorylation, extrasynaptic AMPA receptors move to the synapse facilitating LTP induction (Guire et al., 2008; Opazo et al., 2010). Subsequently, dephosphorylation by CaN induces removal of the synaptic GluA1-AMPA receptors via endocytosis during LTD (Ashby et al., 2004; Lee et al., 1998, 2009). Anchoring of PKC and CaN by AKAP5 (Guo et al., 2015) facilitates activation, rapid endocytosis and exocytosis of AMPA receptors in response to a signal.

As mentioned above, the brain distribution of AKAP5 suggests an eminent role in memory formation. In this respect, induction of LTP *in vivo* caused upregulation of AKAP150 mRNA during L-LTP (Tunquist et al., 2008). Additionally, it was shown that AKAP5 null neurons exhibit altered synaptic plasticity and impaired LTD, due to exclusion of PKA and CaN from the dendritic spines (Genin et al., 2003). In accordance with the important role of LTD in memory formation (Collingridge et al., 2010), AKAP KO mice also exhibit impairments in memory retention (Tunquist et al., 2008). Additionally, both LTP and LTD were abolished in a mouse strain (D36) carrying a truncated version of AKAP5 that prevents binding of PKA (Lu et al., 2007, 2011). These results indicate that D36 mice exhibit a more severe electrophysiological impairment in comparison to AKAP KO mice. This observation was also confirmed in the study of Weisenhaus et al. that additionally examined whether the reported electrophysiological deficits are extended to the behavioral level (Weisenhaus et al., 2010). In their study, D36 mice appear to have more pronounced impairments in reversal learning in an operant conditioning paradigm for food reward in comparison to AKAP KO mice. The differences between the two strains indicate the importance of interaction between PKA and AKAP5 in controlling synaptic transmission.

Accordingly, several studies demonstrated that anchoring of PKA to AKAP5 is critical for maintaining compartmentalized cAMP signaling that subsequently coordinates learning and memory (Poppinga et al., 2014). In that respect, most of the animal studies indicate the importance of PKA-AKAP5 interaction utilizing the fear conditioning paradigm. In the study of Moita et al. the st-Ht31 peptide that competes for the binding site of PKA in the AKAP5 (Dodge and Scott, 2000), was infused in the lateral amygdala of mice and resulted in impaired consolidation of fear memory (Moita et al., 2002). A later study extended these findings showing that AKAP5 is upregulated in the hippocampus of mice during exposure to a novel context, but also at the late consolidation period of fear conditioning memory (Nijholt et al., 2007). Along the same lines, disruption of PKA-AKAP5 anchoring in the hippocampus via the st-Ht31 peptide or the more specific superAKAP-IS peptide prevented late-consolidation, but not acquisition and retrieval of fear memories (Nijholt et al., 2008). Finally, KO of AKAP5 was accompanied with spatial memory retention deficits evaluated with the MWM test in mice (Tunquist et al., 2008).

11. Temporal distinction in cyclic nucleotide signaling: time windows of action

The molecular mechanism underlying different mnemonic stages is a matter of investigation for several years and it still remains elusive. Interestingly, several experimental lines indicate that cyclic nucleotides participate in distinct time windows of memory processes. Specifically, the sGC/cGMP/PKG signaling pathway is involved in the early consolidation phase, while AC/cAMP/PKA signaling is implicated in the late consolidation stage (Izquierdo et al., 2002). An important aspect of this temporal distinction is whether cyclic nucleotides act in parallel or sequential to activate CREB. In other words, does cGMP/PKG signaling at the early phase depend on cAMP/PKA signaling at the late phase of consolidation or do the two signaling cascades act independently during memory formation?

Early work with LTP experiments showed that cGMP/PKG is involved in L-LTP by promoting CREB phosphorylation and Ca^{2+} release from ryanodine stores (Lu and Hawkins, 2002; Lu et al., 1999). These experiments support the notion that the cGMP/PKG pathway acts independently of the cAMP/PKA pathway to promote CREB phosphorylation and eventually protein synthesis required for long-term plasticity. The parallel action of the two pathways was further underpinned by studies conducted in honeybees showing that an externally applied cGMP analog could synergistically activate PKA at the presence of nanomolar concentrations of cAMP (Leboulle and Müller, 2004). Nevertheless, there are studies showing that the two pathways are converging in order to produce long-term plasticity. A study conducted in crickets showed that activation of the NO/cGMP cascade precedes activation of the cAMP signaling pathway for the formation of long-term memory. In fact, it is suggested that NO/cGMP stimulates cAMP activation via CNGC and calmodulin (Matsumoto et al., 2006). Based on the model that the authors proposed, cGMP promotes activation of CNGC leading to increased influx of Ca^{2+} that in turn activates calmodulin. Finally, the Ca^{2+}/calmodulin complex could directly activate ACs, providing the link between the two cyclic nucleotide cascades. Of note, in the cricket study, the cGMP analogs were applied externally. A follow-up study showed that cGMP produced in physiological conditions after a learning paradigm could not activate PKA even in the presence of low levels of cAMP (Matsumoto et al., 2009). The authors suggested that the contradictory findings indicate that cGMP production and PKA activation occur in different subcellular compartments in the same or in different neurons. Therefore, in physiological conditions PKA is inaccessible to cGMP (Matsumoto et al., 2009).

A later study from Bollen et al. in which they targeted cGMP/PKG and cAMP/PKA pathways during specific time windows of plasticity and memory formation, underscored the temporal dissociation of the signaling cascades and, additionally, the cGMP-mediated modulation of the cAMP pathway (Bollen et al., 2014). The electrophysiological study showed that activation of the cGMP/PKG pathway before or 10 min after a weak tetanus-induction protocol could convert E-LTP to L-LTP,

suggesting that both acquisition and early consolidation are cGMP/PKG dependent. The same observation was possible for the cAMP/PKA pathway when it was activated either before or 90 min after the induction protocol suggesting that the cAMP/PKA pathway participates in acquisition and late consolidation processes. At the behavioral level, activation of the cGMP/PKG pathway at the early consolidation time window or the cAMP/PKA pathway at the late consolidation time window could extend STM into LTM, as tested with rats in the ORT. The existence of defined time windows in the action of cyclic nucleotides was outlined from a later study showing that the pro-cognitive effect of upregulating the cGMP/PKG cascade is apparent when it takes place within 45 min after training in the ORT. However, elevation of cAMP/PKA cascade is only effective when it occurs between 3 and 5.5 h after training in this test (Akkerman et al., 2016). Additionally, the previous study of Bollen et al. showed that early activation of cGMP/PKG requires intact cAMP/PKA signaling at the late phase in order to promote L-LTP and LTM. In both electrophysiological and behavioral studies, the plasticity and memory enhancing properties of cGMP/PKG activation were abolished when PKA was blocked at the late phase of LTP or memory formation. On the contrary, PKG inhibition at the early phase of plasticity and memory did not affect the pro-cognitive effect of cAMP/PKA pathway activation at the late phase. These findings suggest that activation of cGMP/PKG at the early phase of plasticity or consolidation requires cAMP/PKA signaling at the late phase for maintaining L-LTP and LTM (Bollen et al., 2014). Importantly, a temporal distinction in the action of cyclic nucleotides can be only made for the consolidation phase, since upregulation of either cGMP/PKG or cAMP/PKA at the acquisition phase has pro-cognitive effects (Fig. 2).

Considering the various experimental procedures and the different complexities of the organisms that have been employed in these studies, it is difficult to draw a conclusion regarding the temporal relationship between cGMP/PKG and cAMP/PKA pathways. Nevertheless, the evidence so far points out that, at least in mammals, these two cyclic nucleotide signaling cascades act in parallel during the acquisition phase, while at the consolidation phase, activation of cGMP/PKG and cAMP/PKA is sequential. This observation raises several questions regarding the mechanistic relationship between the two cyclic nucleotide signaling cascades. For example, by which mechanisms the cGMP/PKG cascade promotes activation of the cAMP/PKA cascade? Considering that PKG inhibition at the early phase of memory consolidation did not affect the pro-cognitive effect of cAMP/PKA at the late consolidation phase, it is unlikely that PKG acts directly on the cAMP/PKA cascade. Nevertheless, it is possible that cGMP promotes cAMP/PKA activation via another downstream effector, like cGMP-regulated ion channels. Additionally, if PKA inhibition at the early phase of LTP and memory consolidation does not affect the pro-cognitive action of cGMP/PKG upregulation, what is the relevance of the immediate peak in PKA activity at the very early phase of a memory task, as was reported in previous studies (Bernabeu et al., 1997a; Mizuno et al., 2002; Vázquez et al., 2000)? A possible explanation is that PKG and PKA share a common downstream effector at this very early phase and therefore concomitant inhibition of PKA and activation of PKG maintain an intact underlying mechanism. Both PKG and PKA phosphorylate the GluA1 subunit of the AMPA receptor at the same serine residue (S845),

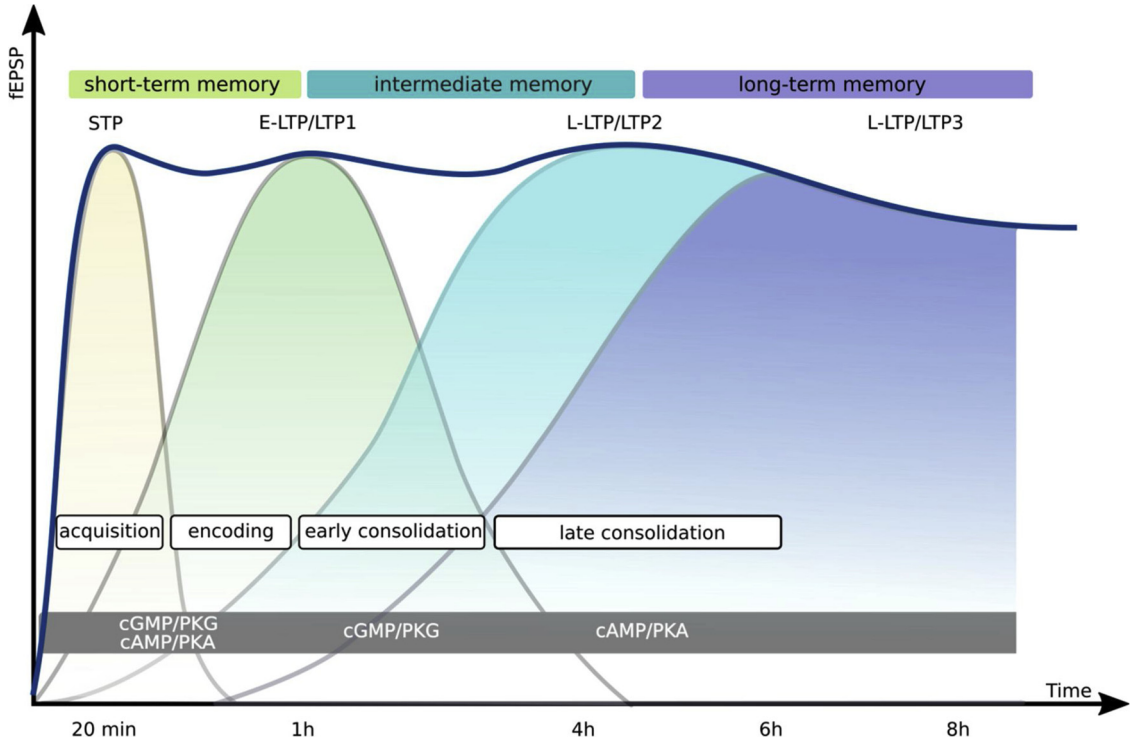

Fig. 2. Schematic representation of the different phases of plasticity and memory. Synaptic plasticity can be divided in the sub-types of short-term potentiation (STP) that typically last less than 1 h and long term potentiation (LTP) that could last up to several hours. LTP can be further divided in early LTP (E-LTP or LTP1) and late LTP (L-LTP). L-LTP is divided into LTP-2 and LTP-3. It is suggested that these sub-types of plasticity represent different memory stages, with E-LTP/LTP-1 being equivalent to short-term memory (STM), LTP2 being related to intermediate memory (IM) and LTP3 underlying long-term memory (LTM). Transformation of one memory stage into another is mediated by the mnemonic process of consolidation. Acquisition is the phase in which sensory information enters the brain. Encoding represents the initial phase of memory formation that is active during acquisition and shortly after, when the information is not present anymore. Consolidation characterizes stabilization of the initial labile memories. It is suggested that the transition of STM to IM and from IM to LTM is mediated by early and late consolidation, respectively. The different stages of plasticity and memory formation are governed by distinct molecular cascades. Both cyclic monophosphate adenosine (cAMP)/ protein kinase A (PKA) signaling and cyclic monophosphate guanosine (cGMP)/ protein kinase G (PKG) signaling are involved during the acquisition phase. Additionally, early consolidation is dependent on activation of the cGMP/PKG signaling pathway, whereas late consolidation relies on activation of the cAMP/PKA cascade. The y-axis represents the magnitude of synaptic plasticity described as field-excitatory postsynaptic potential (fEPSP).

promoting its trafficking into the membrane (Serulle et al., 2007). Thus, it is plausible that this common mechanism could explain the above finding regarding the role of cyclic nucleotides at the very early phase of plasticity and memory formation. Such a common mechanism has been suggested to relate to the memory processes of encoding, which are active during acquisition and continue during a short period after acquisition, i.e. into the actual consolidation window (Akkerman et al., 2015). Finally, what is the therapeutic relevance of the temporal distinction in the function of cyclic nucleotides? Considering that activation of the cGMP/PKG and the cAMP/PKA cascade via, for example, specific PDE inhibitors induces unwanted side effects, combining cGMP- and cAMP-selective PDE inhibitors at low sub-efficacious doses could be a possible alternative treatment (Bollen et al., 2015). In that case, the pro-cognitive effects of upregulating the cGMP/PKG and cAMP/PKA cascade will be maintained, while the unwanted side effects are circumvented.

12. New techniques in detecting, measuring and modulating cyclic nucleotide signaling

So far, we presented data of the last decades indicating the complexity of cyclic nucleotide signaling and the plethora of molecules that orchestrate cAMP and cGMP dynamics and their subcellular distribution. Better understanding of cyclic nucleotide signaling imposed the need for new ways to measure levels of cAMP and cGMP in cells. Biochemical techniques including radio- and immuno-assays can give a relative estimation of the amount of cAMP or cGMP in cell lysates. Nevertheless, these techniques require a large amount of cells or tissue, lack spatiotemporal resolution and cannot provide evidence for the real-time changes in cAMP/cGMP gradients in living cells. The development of optical biosensors based on Förster resonance energy transfer (FRET) significantly improved our ability to measure and monitor cyclic nucleotide signaling (Sprenger and Nikolaev, 2013).

12.1. Application of FRET imaging for detecting cAMP signaling

The first biosensors for detecting cAMP intracellular levels utilized the dissociation of the C and R regulatory subunits of PKA upon cAMP binding. The first cAMP biosensor named “FlCRhR” comprised a fluorescein-tagged C subunit and a rhodamine-labeled R subunit in which binding of cAMP to the R subunit caused dissociation of the subunits and reduction in FRET emission (Adams et al., 1991). A few years later, Zaccolo et al. developed a genetically encoded cAMP biosensor in which the R or the C subunit of PKA was fused with a fluorescent probe (Zaccolo et al., 2000). Although utilization of FlCRhR provided information about the spatial distribution of cAMP/PKA during stimulation of sensory neurons in Aplysia (Bacskai et al., 1993), and the PKA-based biosensor was proven useful in unraveling cAMP signaling dynamics and compartmentalization in rat cardiac myocytes (Zaccolo and Pozzan, 2002), their application was restricted due to technical difficulties. For example, transfection of the whole holoenzyme in the case of FlCRhR was not feasible in neurons, while PKA biosensors required transfection of both plasmids and equal subunit distribution in the cytosol.

The discovery of Epacs as additional downstream effectors of cAMP signaling, led to the development of singled-chained Epac-based biosensors. Both Epac1 and Epac2 were fused with cyan-fluorescent protein (CFP) at the N-terminus and yellow-fluorescent protein (YFP) at the C-terminus to generate the first Epac1 and Epac2 biosensors. Binding of cAMP to the biosensor introduces conformational changes reducing yellow to cyan emission and therefore decreasing FRET (DiPilato et al., 2004; Nikolaev et al., 2004; Ponsioen et al., 2004). Fusion of Epac1-camps to the N-terminal domain of the different PKA subunits led to PKA-RI- and PKA-RII-specific FRET biosensors (Wachten et al., 2010). As it was shown before, PKA-RI and PKA-RII are tethered to distinct cellular compartments via AKAPs. These compartments generate spatially distinct modulation of intracellular signaling cascades in response to extracellular stimuli (Wachten et al., 2010). Utilization of PKA-RI and PKA-RII biosensors in rat myocytes revealed a microdomain-specific regulation of cAMP levels mediated via different PDEs (Stangherlin et al., 2011). In these cells, simulation of the β-AR generates a spatially restricted pool of cAMP that mainly activates PKA-RII and to lesser extend PKA-RI. Increased production of cGMP via stimulation of sGC promotes activation of PDE2 that is in close proximity to the PKA-RII pool and inhibition of PDE3 that resides close to PKA-RI, reversing the PKA-defined cAMP gradient (Stangherlin et al., 2011). Additionally, Epac2-camps tagged to AC8 (Epac2AC8^{D416N}) helped to identify distinct pools of cAMP microdomains associated with AC activity in pituitary cells (Wachten et al., 2010). Worth mentioning is that Calebiro et al. generated a transgenic mouse line (GAG-Epac1-camps) that expresses an Epac1 biosensor ubiquitously allowing examination of cAMP signaling in a more physiological context (Calebiro et al., 2009).

The most well-known Epac-based probes are called ICUE (indicator of cAMP using Epac), and so far there have been developed three versions of the construct (ICUE1-3) with progressively improved properties (DiPilato et al., 2004; Liu et al., 2012; Marley et al., 2013). ICUE1 constructs that were modified to be expressed in the plasma membrane, mitochondria and the nucleus revealed the dynamics and the propagation of cAMP signaling in the subcellular compartments in response to adrenergic stimulation (DiPilato et al., 2004). ICUE3 probes targeted to the nucleus provided a first indication of the role of the nuclear PKA holoenzyme, showing that it is activated in response to sAC (Sample et al., 2012). Additionally, utilization of ICUE3 probe revealed a novel role of the actin binding protein coronin 1 in modulating synaptic plasticity and neurobehavioral processes via potentiation of the cAMP/PKA pathway (Jayachandran et al., 2014).

An alternative approach to detect cAMP signaling is via the A-kinase activity reporter (AKAR). This family of biosensors contains a PKA substrate sequence and a phospho-binding domain sandwiched between 2 fluorescent proteins (eCFP and YFP/Venus). Increased PKA activity leads to phosphorylation of PKA substrate and subsequent binding to the phospho-domain increasing FRET. The study of Gervasi et al. in which they used AKAR2, showed the differential amplitude and time course of PKA signal integration from membrane to the nucleus in response to AC or GPCR stimulation (Gervasi et al., 2007). Additionally, utilization of AKAR2 provided evidence showing that anchoring of PKA, AC5 and AC6 by AKAP150/79, facilitates a negative feedback mechanism that reduces cAMP production (Bauman et al., 2006). Along similar lines, a study from Schott et al. in which they targeted AKAR3 to the plasma membrane or the cytosol, reported that gravin (or AKAP12) impacts subcellular PKA activity levels through the spatial targeting of PKA in response to Ca^{2+} elevation. The above results support the hypothesis that gravin mediates crosstalk between Ca^{2+} and PKA-dependent signaling pathways (Schott et al., 2016). A modified version of AKAR4 that was targeted at lipid raft and non-raft regions of the plasma membrane gave first insight into the compartmentalization of PKA activity in the different microdomains in the membrane (Depry et al., 2011). Additionally, Epac1, Epac2 and AKAR2 biosensors revealed differential regulation of the cAMP/PKA pathway in response to β-AR stimulation in two different compartments of the cell; the bulk cytosol of the cell bodies and the submembrane domain of the thin dendrites (Castro et al., 2010). Specifically, the amplitude of the cAMP/PKA response in the cell soma was weaker in comparison to the thin dendrites, supporting modeling predictions showing that the surface to volume ratio affects cAMP dynamics (Neves et al., 2008). Accordingly, biosensor imaging in mouse brain slices showed that cAMP/PKA signaling differs between striatal and cortical neurons, with the first exhibiting faster and longer-lasting responses to stimuli that elevate cAMP/PKA pathway (Castro et al., 2013). This difference could be attributed to several parameters including enhanced PDE4 activity in the cortex and stronger AC activation in the striatum (Castro et al., 2013).

Recently, imaging of PKA activity in brain tissue has been

established by the development of PKA-based biosensors that are compatible for 2-photon microscopy. Fluorescence Lifetime Imaging Microscopy (FLIM) represents a revolutionary approach of FRET imaging that promises to overcome limitations that did not allow FRET imaging in thick brain tissue (van Munster and Gadella, 2005; Wallrabe and Periasamy, 2005). For instance, a study from Chen et al. reported that a FLIM-AKAR biosensor could detect changes in PKA activity in the soma and the dendrites of CA1 neurons in response to GPCR activation and AC stimulation (Chen et al., 2014a). Importantly, implementation of two-photon fluorescence lifetime imaging microscopy (2pFLIM) coupled to an optimized AKAR variant (tAKARα sensor) unable researches to track bidirectional PKA activities in individual neurons in awake mice and reveal neuromodulatory PKA events that were associated with wakefulness, pharmacological manipulation, and locomotion (Ma et al., 2018).

12.2. Application of FRET imaging for detecting cGMP signaling

The development of cGMP FRET probes was based on the utilization of a cyclic nucleotide binding domain derived from PKG or cGMP-specific PDEs fused within two fluorophores forming a FRET pair. A challenge in the development of cGMP probes was achieving high specificity for the probes, because the levels of cGMP in a cell are lower than the levels of cAMP. The first PKG-based biosensor, called Cygnet-1 (cyclic GMP indicator using energy transfer), was comprised by a truncated version of PKGIα at the N-terminus fused between CFP and YFP, while Cygnet-2 was the catalytically inactive variant of Cygnet-1 (Honda et al., 2001). In both probes, binding of cGMP led to decreased FRET. The development of Cygnet biosensors contributes to our knowledge regarding the dynamics and the regulation of cGMP signaling in various cell types (Cawley et al., 2007; Mongillo et al., 2006; Takimoto et al., 2005). In the brain, the use of Cygnet in thalamic neurons showed that although they express PDE1, 2, 9 and 10, basal cGMP concentration is mainly regulated by PDE2 activity (Hepp et al., 2007). Additionally, Cygnet was used in combination with an Epac-based sensor (EPAC-SH^{150}) to disentangle the role of cyclic nucleotide signaling in medium spiny neurons (MSNs) in the striatum (Polito et al., 2013). The study showed that cGMP signaling could reduce cAMP signaling through activation of PDE2 in the MSNs (Polito et al., 2013).

Despite the fact that Cygnet biosensors enable the monitoring of cGMP levels and extend our knowledge regarding cGMP signaling, they exhibited low dynamic range and temporal resolution. Nikolaev et al. developed three shorter cGMP biosensors containing a single cGMP-binding domain from PKGIα (cGES-GKIB) or the GAF domain from PDE2 (cGES-DE2) or PDE5 (cGES-DE5) (Nikolaev et al., 2006). Binding of cGMP decreases the FRET signal in case of the PKGIα-based biosensor, while the FRET signal increases in the case of PDE-based biosensors. Replacement of CFP/YFP in the cGES-DE5 sensor by a red (Dimer2) and green (T-Sapphire) fluorescent protein allowed simultaneous imaging of two FRET sensors (i.e. cAMP and cGMP biosensors) in the same cell (Niino et al., 2009). Surprisingly, the replacement of the fluorescent pair increased its affinity for cGMP by 40-fold, making it the most promising sensor for measuring real-time cGMP concentration in living cells (Niino et al., 2009). A few years later, a new series of cGMP biosensors was developed, i.e. cGi-500, cGi-3000, cGi-6000, with EC_{50} of 500 nM, 0.3 μM and 0.6 μM, respectively. These biosensors exhibit high selectivity for cGMP and a better dynamic range than the previous cGMP biosensors (Russwurm et al., 2007).

In an effort to increase the sensitivity for cGMP biosensors, Nausch et al. developed non-FRET biosensors named FlincGs (fluorescent indicators for cGMP). These biosensors (α-FlincG, β-FlincG, and δ-FlincG) contain a truncated cGMP binding domain from PKGIα or PKGIβ flagged with a circularly-permuted enhanced GFP (cpEGFP), and binding of cGMP increases the fluorescence emitted by cpEGFP (Nausch et al., 2008). Finally, a recent cGMP biosensor was constructed containing the GAF-A domain of PDE5 fused between a blue fluorescent donor and a dark fluorescent acceptor. The development of this biosensor permitted triple parameter fluorescent imaging utilizing the blue fluorescent cGMP biosensor, a CFP/YFP cAMP sensor and a red fluorescent probe for Ca^{2+} in a single cell (Niino et al., 2010).

Worth mentioning is that FRET sensors have been developed for detecting levels of cyclic nucleotides in close vicinity of PDEs. Specifically, Herget et al. fused Epac1-camps or cGES-GE2 to the N-terminus of PDE3A, PDE4A1 or PDE5A (Herget et al., 2008). These sensors allow detection of differences in cAMP and cGMP gradients around PDEs and contribute to a better understanding of PDE activity in cellular processes and in the compartmentalization of cyclic nucleotide signaling. Additionally, these sensors were used for evaluating the effect of selective PDE inhibitors in the local pools of cAMP gradients and compare their different pharmacokinetic properties (Herget et al., 2008).

12.3. Modulation of cAMP and cGMP signaling via optogenetics

Despite these techniques for detecting cyclic nucleotide signaling in living cells, the need to actively modulate neurons with high temporal resolution remained. The expanding toolbox in neuroscience techniques gave researchers the opportunity to modulate neurons via light. The technique of optogenetics is based on the presence of photosensory domains in light-sensing organisms. The initial optogenetic studies in the nervous system used the light-gated ion channels channelrhodopsin (ChR) and halorhodopsin (HR) to gain more insight into molecular cascades and networks that are activated during neuronal plasticity (Boyden et al., 2005; Zhang et al., 2007). Coupling of a photoreceptor domain to different effector domains of cAMP or cGMP permits optogenetic manipulation of cyclic nucleotide signaling. Specifically, absorbance of light from the chromophore in the synthetic light-responsive system induces a conformational change that activates the effector domain. The responsiveness of the system in the different light spectra depends on the photoreceptor domain. Common chromophores used in the development of optogenetics tools are the light-oxygen-voltage-sensing (LOV) domain and the blue light utilizing flavin (BLUF) domain.

The first photoactivated adenylate cyclase (PAC), named euPAC, was identified in *Euglena gracilis* in which it was serving a role in photoavoidance. This AC has a heterotetrameric structure consisting of two PACα and PACβ that are activated by blue light and four catalytic domains homologous to group III ACs (Iseki et al., 2002). The functional expression of PACα and PACβ was verified in different systems including *Xenopus laevis* oocytes, HEK293 cells, *Aplysia* and *Drosophila melanogaster* (Nagahama et al., 2007; Schröder-Lang et al., 2007). The large size and high basal activity in the dark after *in vivo* expression prevented the wide application of euPAC in other organisms. Another PAC, named BlaC, was constructed by Gomelsky and colleagues. The construct was containing the *blaC* gene encoding a group III AC isolated from *Beggiatoa* sp. and one BLUF domain, reducing the size significantly (Ryu et al., 2010). Around the same time the group of Hegemann validated the efficacy of the same protein, which they named bPAC (Stierl et al., 2010). In *Escherichia coli* and *Xenopus* oocytes, bPAC showed low cyclase activity in darkness that is increased by 300-fold in the light. Additionally, the applicability of bPAC was validated in rat cortical neurons (Stierl et al., 2010), *Drosophila* nervous system (Efetova et al., 2012; Stierl et al., 2010) and zebrafish (De Marco et al., 2013, 2016; Gutierrez-Triana et al., 2015). More recently a blue light-regulated AC was identified in *Microcoleus chthonoplastes*, named mPAC. This enzyme contains a photoreceptive LOV domain and exhibits higher constitutive activity in comparison to euPAC and BlaC/bPAC, but also higher activity after blue light irradiation (Chen et al., 2014b; Raffelberg et al., 2013). Although the promising dynamic range, extensive use of these PACs was restricted due to disadvantages in the use of blue light including low tissue penetration and photooxidative damage (Hockberger et al., 1999). The first synthetic PAC that is activated in the near-

infrared window (NIRW) was engineered by the group of Gomelsky (Ryu et al., 2014). The Ilac construct was containing a photosensory module from the *Rhodobacter sphaeroides* bacteriophytochrome DGC, BphG1 and a typre III AC domain from the Nostoc sp. CyaB1 protein. The effectiveness of Ilac was tested in cholinergic neurons of *Caenorhabditis elegans* in which exposure to red light altered the locomotor behavior of the animal indicating elevation in cAMP/PKA signaling (Ryu et al., 2014). Importantly, generation of NIRW-activated ACs provides the opportunity of combinatory imaging techniques for detecting or manipulating cyclic nucleotide signaling.

The first photoactivated GC was constructed by multiple mutations in the *Beggiatoa* BlaC. The triple mutant, designated BlgC, was shown to exhibit GC activity *in vitro* and irradiation with blue light resulted in significant increase in cGMP production *in vivo* (Ryu et al., 2010). The first natural light-activated GC was identified in fungus *Blastocladiella emersonii* by the group of Gomes (Avelar et al., 2015; Scheib et al., 2015). The BeGC1, as it was named by the Gomes group, consists of rhodopsin fused to a GC catalytic domain and is activated by green light. The efficacy of the enzyme was confirmed in *in vitro* and *in vivo* assays including HEK293 T cells, *Xenopus* oocytes, muscle cells of *Caenorhabditis elegans*, mammalian ovary cells and cortical neurons (Scheib et al., 2015). Additionally, Gomelsky's group engineered a NIRW-activated construct for the production of cGMP (Ryu and Gomelsky, 2014). The chimeric construct was comprised of a bacteriophytochrome c-di-GMP synthase (diguanylate cyclase, DGC) originating from the *Rhodobacter sphaeroides* BphG1 protein and a constitutive c-di-GMP-specific PDE, YhjH from *E. coli*. DGC is not expressed in higher eukaryotes and could allow orthogonal regulation of c-di-GMP signaling in mammals (Ryu and Gomelsky, 2014).

A different angle in the attempt to manipulate the cyclic nucleotide signal constituted the engineering of light-activated PDEs (LAPD). The first photoactivated PDE was comprised of the photosensor module of *Deinococcus radiodurans* bacterial phytochrome and the effector module of the human phosphodiesterase 2A (Gasser et al., 2014). The photoactivated construct has dual substrate specificity and illumination with red-light could enhance the hydrolysis of cGMP and cAMP by 6-and 4-fold, respectively. Additionally, exposure of LAPD to far-red light could decrease its activity. The efficacy of LAPD in increasing hydrolysis of cyclic nucleotides was established in eukaryotic cell cultures and zebrafish embryos (Gasser et al., 2014). Although LAPD appears promising for studies in living organisms, the dual specificity of the enzyme does not allow distinction between the action of cAMP and cGMP. An enzyme with PDE activity was isolated from the choanoflagellate *Salpingoeca rosetta* almost at the same time by the Kandori and the Oprian groups (Lamarche et al., 2017; Yoshida et al., 2017). The Rh-PDE or RhoPDE, as it was named by the different groups, is a fusion of rhodopsin type I with PDE. The enzyme displays only a minimum amount of light-dependent PDE activity and can hydrolyze both cyclic nucleotides constitutively in the dark, but with higher selectivity for cGMP over cAMP (Lamarche et al., 2017; Yoshida et al., 2017). Crystallography of the isolated PDE domain of the enzyme showed high resemblance in terms of sequence and structure to the human PDE9 (Lamarche et al., 2017). Future research will provide better insight in the function of this unique fusion protein and its potential use as optogenetic tool in modulating cyclic nucleotide signaling.

13. Discussion

The above studies indicate that development of treatments targeting the cyclic nucleotide signaling cascades could be a promising approach for combating memory impairments. Nevertheless, it is still a matter of intense investigation which components should be targeted in memory-related diseases. Proper memory formation is based on a well-orchestrated balance between production and degradation of cyclic nucleotides, as well as, positive and negative feedback mechanisms. In AD, the rationale for upregulating the AC-cAMP-PKA/Epac or the sGC-cGMP-PKG signaling cascades is based on the observation that CREB activation is negatively affected in the progression of the disease (Yamamoto-Sasaki et al., 1999). Since these cascades promote CREB phosphorylation, they could represent a compensatory approach resulting in increased phosphorylation of CREB. However, upregulation of a system, even one that potentially possesses pro-cognitive function, does not result in memory improvement *per se*. For example, genetic deletion of G_{ia1}, that inhibits adenylate activity in the hippocampus, enhances LTP, but also results in severe memory deficits in several cognitive tasks (Pineda et al., 2004). This result indicates that disrupting the "break" of AC activity causes a saturation of cAMP production in the hippocampus that leads to signal desensitization preventing formation of new memory (Pineda et al., 2004). Similarly, overexpression of AC1 results in impaired extinction of previously acquired memories which indicates synaptic deficit (Wang et al., 2004). On the other hand, pharmacological interventions like, for instance, preventing degradation of cyclic nucleotides by PDE inhibitors seems to represent a more balanced approach in modulating cyclic nucleotide concentration and improving cognitive function, yet caution is also needed here (see below; 53, 54). A possible explanation could be that in the case of a genetic approach there is complete depletion of a molecule, while in the case of pharmacological intervention there is a partial inhibition/stimulation, thus a more subtle influence on cellular signal transduction. Future studies will have to reveal the exact role of cyclic nucleotide signaling cascades in neuroplasticity and memory formation, as well as the full potential of targeting the cyclic nucleotide signaling cascades in pathological conditions.

Another important consideration is the altered biochemical signals in a diseased or aged brain. As it was reported before, the PKA signaling cascade appears over-activated in the prefrontal cortex of aged animals (Arnsten et al., 2005). Therefore, mild activation of the cAMP/PKA signaling cascade with cAMP-specific inhibitors or PKA activators could exacerbate the cognitive performance related to prefrontal cortex. Nevertheless, there is no evidence reporting a similar effect for Epacs. Another line of studies showed that sGC responsiveness to NO is decreased in the temporal lobe of AD patients (Bonkale et al., 1995). A possible approach to reduce the side effects of the disinhibited PKA signaling cascade in the PFC and other adverse side effects could be combination of drugs that act on different cascades. In this respect, it was recently shown that co-administration of sub-efficacious doses of PDE4 and PDE5 inhibitors could improve mnemonic process in physiological conditions, but also rescue memory impairments in an animal model for AD (Bollen et al., 2015; Gulisano et al., 2018). Additionally, the usage of sGC activators could overcome the lack of sGC responsiveness encountered in diseases like AD. These observations indicate the importance of taking into account age-related changes in expression and function of cyclic nucleotide signaling molecules when developing therapies for the treatment of memory diseases.

An integral part in the development of new therapeutic strategies is the in-depth understanding of the molecular mechanisms conveying memory processes. Development of new optical methods broadened our knowledge regarding the physiological action and compartmentalization of different molecules involved in the cyclic nucleotide cascades. Despite the sensitivity of these techniques, they are usually implemented in isolated cells or tissues. Although the cyclic nucleotide cascades are presented conventionally to be linear, the relationship of their signaling molecules deviates from linearity with the presence of several positive or negative loops. Additionally, several isoforms of the signaling components are characterized by region and even sub-cellular specificity in their distributions. These characteristics impede accurate prediction of the exact molecules that would be activated in a specific brain domain upon administration of a drug that acts on the cyclic nucleotide pathways. Therefore, the implementation of computational models is eminent for integrating experimental data with other parameters including domain distribution, diffusional rates, interactions with other pathways and enzyme kinetics for the cyclic nucleotides

signaling networks. For example, development of stochastic models was used to reveal the temporal patterns by which CaMKII and PKA are active during L-LTP and the importance of colocalization of PKA with its downstream effectors in subcellular microdomains for maintenance of L-LTP (Kim et al., 2010, 2011).Cyclic nucleotide signaling cascades modulate a vast array of physiological and pathophysiological processes via their regulation of the intracellular second messenger molecules, cAMP and cGMP. Despite a century of research into exactly how they exert their function in these processes, we are only starting to comprehend their multifactorial interactions and the complexity of signaling networks that they constitute in the brain. Emerging understanding of the functional roles of these cyclic nucleotide pathways in compartmentalized signaling brain networks, together with the ongoing development of the neuroscience tool box, including genetic models, optical techniques and predictive computational models, provides great potential for cyclic nucleotide signaling molecules to emerge as a promising target for the development of cognitive enhancing therapies for several brain disorders, including memory dysfunction as observed in AD patients.

Conflict of interest statement

JP has a proprietary interest in the PDE4 inhibitor roflumilast.

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